PYRIDINE ALCOHOLS AND THIOLS

Synthesis, Properties and Applications

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	Prof. Dr. J.H. Teuben

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Voor Gertrude en Lisa

Aan mijn ouders

Voorwoord

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CHAPTER 1

1.1 Enzymes and Mimics Thereof.

Enzymes, the catalysts provided by Nature, perform a large number of tasks in biological systems. However, their applications in synthetic chemistry and in particular large-scale manufacturing are subject to limitations owing to the many aspects of enzyme catalysis such as the role of the metal in metallo-enzymes, the recognition processes, substrate binding, the process of covalent bond breaking and forming, allosteric effects and enzyme regulation, product release and protein degradation. Despite many decades of intense study, for the majority of classes a full description of enzyme catalysis at the molecular level remains to be achieved. On the other hand at one level, as suggested by Pauling, enzyme catalysis can be explained: what an enzyme does is bind the substrate and thus lower selectively the transition state for a particular reaction.[1] This principle should be applicable to nonnatural systems as well. Despite this knowledge, the design and synthesis of artificial enzyme systems for industrial purposes with catalytic activities that rival those of natural enzymes still remains an objective seldom achieved. Understanding of enzymes on the one hand is based on mechanistic work on enzymes and on the other hand based on studies of binding and catalysis of simpler (artificial) systems. Because of the structural complexity of enzymes much work has been done in a reductionist approach wherein an attempt is made to model only the essential features of the active site. Although these primitive synthetic models are far different from enzymes they can contribute insight into the enzyme mechanism and its important structural features. Furthermore such mechanistic insight can lead to development of new catalysts for (enantioselective) transformations.

Although enzymes are highly evolved catalysts, they in some instances, recognize and respond to molecules other than their specific substrate and product although usually with appreciable loss of activity. Catalysts for synthetic chemistry usually do not need the high substrate specificity that enzymes require (high enantioselectivity, however, is very desirable). In a chemical reactor the catalyst does not have to select its substrate from many hundreds of compounds in the same solution as enzymes must in a cell. A sensible

design strategy for enzyme mimics as effective synthetic catalysts is minimalist, only those features of enzymes that are essential for catalytic efficiency are considered. The enzyme mimics are unnatural and are often constructed of non-peptidic molecules although the structural design is aimed at mimicking the behavior of natural enzymes. The structure of these molecules, at least in principle, can be controlled through systematic structural changes, making it possible to investigate the features required for enzyme-like catalysis. Designing a mimic is not a simple task since criteria for activity are very restrictive: a binding site corresponding to the active site of the enzyme must be present and a reaction must then be possible within it. One enzyme that has been a subject of interest for many years in our group is horse liver alcohol dehydrogenase.

1.2 Horse Liver Alcohol Dehydrogenase.

Horse liver alcohol dehydrogenase (HLADH) belongs to the group of oxido-reductases. These catalyze the interconversion of alcohols and aldehydes, making use of the coenzyme nicotinamide adenine dinucleotide (NAD^+/NADH).[2] HLADH can exists as two homodimers or one heterodimer –there are two distinctive types of subunits, denoted E (for ethanol-active) and S (for steroid-active), which differ in relative substrate specificities.[3] Both subunits consist of 374 amino acids and both contain two firmly embedded zinc atoms and one active center. These subunits differ only in six residues, of which one determines E or S activity, namely a phenylalanine (E) or a leucine (S) in position 110.[4] With these two subunits three combinations, isoenzymes, are possible (EE, SS and ES).[5] When isolated from liver, 40-60% of the enzyme is in the EE form.

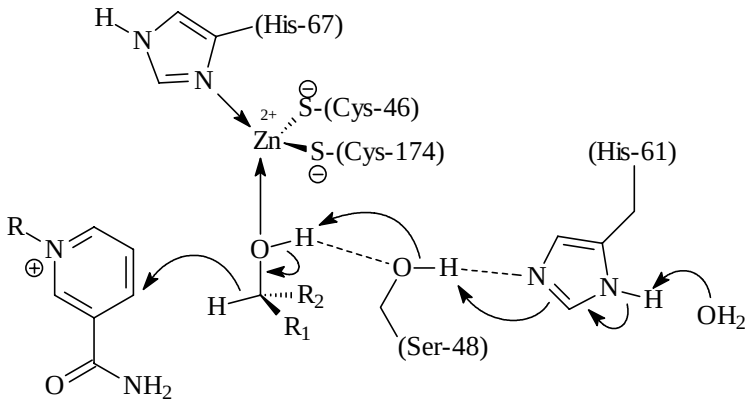


Figure 1.1 *Schematic overview of the active site of HLADH.*

Of the two zinc ions in the enzyme only one is ligated in the active site.[6] The other is coordinated by four cysteine sulfur atoms and is though to have a structural function only.[7]

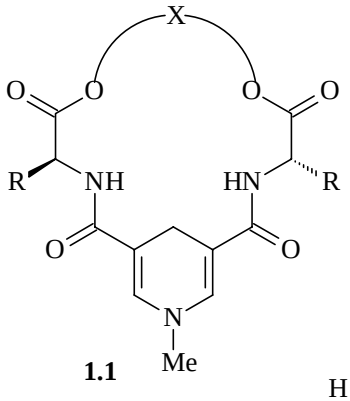
The zinc atom in the active site (see Figure 1.1 for structure and postulated mechanism) is coordinated by two cysteine sulfur atoms (Cys-46 and Cys-174) and one nitrogen from histidine (His-67). The fourth coordination site is occupied by a water molecule or hydroxyl ion (depending on the pH) that is hydrogen bonded to a serine (Ser-48). This zinc ion is situated at the junction of two binding sites: one of these is a pocket, which binds NAD^+, whereas the other is a cleft, which binds the substrate. In the reaction cycle the coenzyme first enters the pocket, causing conformational changes in the enzyme as a result of which the active site loses most of its water.[2,6b,8] The substrate molecule can now bind in the cleft, where it is activated by polarization of the C–O bond by binding of the zinc ion, by hydrogen bonding with a serine OH group and by the positive charge of the coenzyme.[9] The actual reaction then occurs.

1.3 Modeling of HLADH.

Modeling of HLADH has in essence followed two different strategies. The most fruitful strategy so far has been the mimicking the catalytic activity using derivatives of 1,4-dihydropyridines. The second strategy has been based on the role of the zinc ion itself. An ideal model would combine both strategies.

Mimicking of the activity of HLADH using NADH models has led to some interesting compounds.[10] Various Hantzsch esters,[11] 1,4-dihydronicotineamide derivatives,[12] 1,4-dihydro-3,5-pyridinecarboxamide derivatives,[11b,13] chiral substituted dihydropyridines,[14] quinoline type-NADH models,[15] sulfinyl dihydropyridines[16] and macrocyclic NADH models[17] have been prepared and investigated. These model compounds are able to reduce phenylglyoxylate esters, ketones, aldehydes and imines in high yields and moderate to high enantioselectivities. Most reductions are performed with Mg^{2+} as metal activator although in some cases Zn^{2+} has been used.[16a] High enantioselection in the reduction of phenylglyoxylate was obtained using chiral bridged dihydropyridines **1.1** developed by *Kellogg* and co-workers.[18] The open chain analogues were found to give much lower selectivities.[13a] High enantioselectivities were also found for bis(NADH) model compounds.[19] These compounds are thought to form a cavity in which the metal ion is embedded. Reaction times in the reduction of ketones with these systems are very long, 1-14 days in general. Davies and co-workers developed a chiral organometallic NADH model **1.2** that allows reduction of phenylglyoxylate esters in 90

min at room temperature with an ee of 98%.[20] Even faster reduction was achieved by *Bourguignon* and co-workers who developed a bicyclic NADH model **1.3** that is able to reduce phenylglyoxylate esters in 15 min with an ee of 94%.[21] Absolute enantioselection (>99 % ee) and high reactivities were reported recently by *Ohno*, who used quinoline type NADH models **1.4** for the reduction of methylbenzoylformate.[22]



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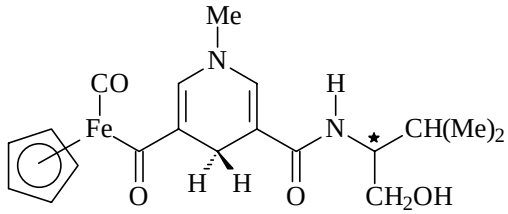

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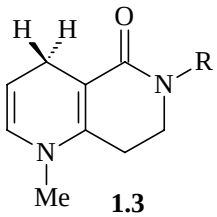

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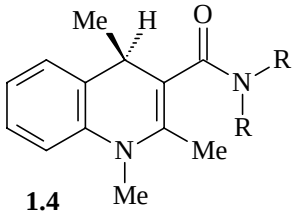
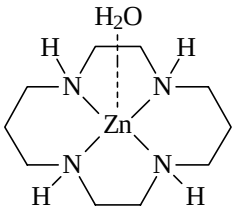


1.4

The second strategy that has been followed for mimicking HLADH is modeling of the catalytic active zinc ion. Synthetic modeling studies with a zinc macrocyclic polyamine complex **1.5** revealed a pK_a drop of an alcohol when it binds to the zinc so that deprotonation occurs spontaneously. [23] However, with thiolates in the coordination sphere one would expect the Zn ion to be a poorer Lewis acid. The influence of the thiolate was studied by Shoner *et. al*.[24] *Parkin* studied the exchange of water with ethanol making use of a tris(pyrazolyl)hydroborato zinc hydroxide system.[25] Earlier the group of Parkin mimicked the coordination of the catalytic zinc of HLADH using a bis(thioimidazolyl)(pyrazolyl)hydroborato zinc complex.[26] A model with a closer resemblance to the natural system was developed by *Curtis et. al*.[27] This model **1.6** consists of two coordinating sulfides and one nitrogen either from a pyridine or imidazole (not illustrated). This model is able to induce reduction of the ketone functionality in the presence of a 1,4-dihydronicotineamide. The interaction of alcohol with zinc thiolates were investigated by *Kovacs*.[28] The best model for the catalytic active zinc in HLADH is expected to feature an incomplete coordination sphere of zinc in which zinc is coordinated by two thiolates and one nitrogen. The fourth coordination site should be filled with a solvent molecule that can exchange with a substrate molecule. However, this

type of coordination is uncommon. The majority of known examples of zinc thiolates are oligomeric owing to the pronounced tendency of thiolates to act as bridging ligands.[29] A monomeric complex **1.7** of zinc, triligated by a pyridine dithiol has been described, however.[30] The steric hindrance caused by the large fluorenyl groups apparently is sufficient to prevent dimerization. Although this model closely resembles the natural active site of HLADH no catalytic activity was observed. The complex decomposes fairly readily and the zinc ion is also likely so deeply embedded that it cannot act as catalyst. could afford some interesting models compounds for HLADH. Therefore a new methodology for the synthesis of pyridine dithiols has to be developed.



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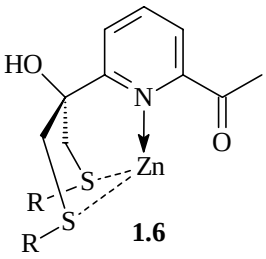

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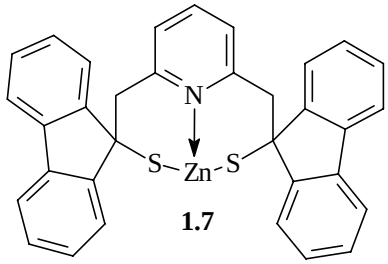
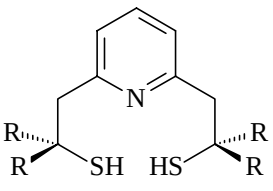


1.7

1.4 Pyridine Dithiols and Diols.

Pyridine dithiols with the generic structure **1.8** are interesting candidates for studies of metal complexes of relevance to the functioning of the zinc ion in horse liver alcohol dehydrogenase. Tuning of the steric hindrance in the pyridine dithiols by variation of the side groups could afford stable complexes with zinc if these substituents are bulky enough to prevent dimerization. The synthetic approach that was used by Berg[31] and Kaptein[30b] does not allow placement of substituents other than phenyl groups. Another method for the synthesis of the tetramethyl pyridine dithiol (R=Me) starting from the tetramethyl pyridine diol **1.9** (R=Me) was developed. This method, however, is restricted to this specific dithiol. Therefore a new, more straightforward method for the synthesis of pyridine dithiols had to be developed.



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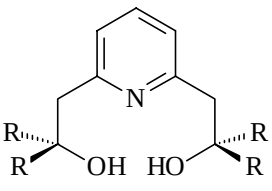

1.9

The pyridine diols **1.9** are also interesting compound based on their ability to form complexes with various metals[32] like Os, Zr, W, Mo, Ti, Zn, Co, Si and Ru and therefore could be of special interest as complexing agents for the development of new homogeneous catalysts. Synthetic approaches thus far give rise to low yields of the pyridine diol and improvement of the synthesis would be desirable. Furthermore our hope is that development of chiral pyridine diols will have positive ramifications for asymmetric catalysis in general.

1.5 Aim of this Study and Survey of this Thesis.

The aims of this research have been the investigation and improvement of the known synthetic approach to pyridine diols as well as development of chiral non-racemic pyridine alcohols. Additionally the development of a procedure for the synthesis of chiral as well as achiral pyridine dithiols using a straightforward addition to thioketones. These new pyridine dithiols were to be investigated as model ligands for the catalytic zinc ion in the enzyme horse liver alcohol dehydrogenase as well as catalysts in various reactions. Furthermore application of the synthetic procedures for derivatization of 2,9-dimethylphenanthroline and 6,6'-dimethyl-2,2'-bipyridine has been an objective.

A brief survey of the enzyme HLADH and models thereof as well as a short introduction on pyridine diols and dithiols is given in Chapter 1. Chapter 2 is devoted to the chemistry of pyridine diols. The possibilities with these ligands are discussed and methods for improving chemical yields are given. C_s-symmetrical pyridine diols have been shown to be side products and a mechanism based protocol for exclusion of their formation is given. Chiral pyridine diols based on camphor, menthone and fenchone have been prepared. Chapter 3 deals with a new synthetic strategy for the preparation of chiral as well as achiral pyridine thiols and dithiols. Complexes of pyridine diols and pyridine dithiols with zinc ions and acids like HCl and HBr are discussed in Chapter 4. The use of pyridine sulfides and disulfides in palladium catalyzed allylic substitution is discussed in Chapter 5. The role of the methyl group on the pyridine ring seems to be very important for the enantioselection in this reaction. The application of the pyridine alcohols and thiols as catalysts for the addition of diethylzinc to aldehydes using a combinatorial approach is described in Chapter 6. Furthermore the use of pyridine diols as ligands for polymerization catalysts is described. This work has been carried out by Marco Bouwkamp. In Chapter 7 the use of pyridine dithiols as model for the active zinc in HLADH and new NADH linked models is reported. Derivatization of phenanthrolines

and bipyridines is discussed in Chapter 8. Chiral as well as achiral ketones were allowed to react with neocuproine after lithiation and exchange of the lithium with $CeCl_2$.

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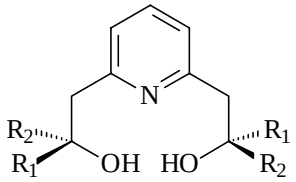
CHAPTER 2

Synthesis of Pyridine Alcohols.*

Abstract: Base induced reaction of 2,6-dimethylpyridine (2,6-lutidine) **2.2** with two equivalents of various ketones has been reported to provide C_2-symmetrical pyridine diols **2.1**. It was observed that best overall yields of the C_2-symmetrical pyridine diols were obtained on application of a two-step, two-pot reaction in which the mono derivatized pyridine **2.3** is isolated and further converted to the diol **2.1**. Long reaction times were found to be essential for a high yield. Closer examination of the reaction revealed that competitive diaddition to a single methyl group can occur to give C_s-symmetrical pyridine diols **2.7**. Not all of these C_S-symmetrical pyridine diols are stable and isolation is complicated by retro addition. By varying the lithiation times the formation of this side product could be maximized or minimized on the basis of a mechanistic proposal for the competing pathways. The formation of C_S-symmetrical pyridine diols **2.7** could be excluded completely by using potassium diisopropylamide as base; high yields of C_2-symmetrical pyridine diols **2.1** are obtained. Selective synthesis of C_S-symmetrical pyridine diols **2.12** was obtained by a base induced reaction of 2-picoline with two equivalents of a ketone. Again, some C_S-symmetrical pyridine diols were found to be labile and retro addition occurred. Chiral non-racemic C_2-symmetrical pyridine diol **2.1e** was synthesized through facially selective addition to (*R*)-camphor. Facially selective addition to fenchone and menthone was achieved using *n*-BuLi as base followed by transmetallation of the lithiated lutidine **2.16** with $CeCl_3$·THF. Pyridine triols **2.18** and **2.19** were synthesized either from pyridine diols **2.1b** or **2.7b**

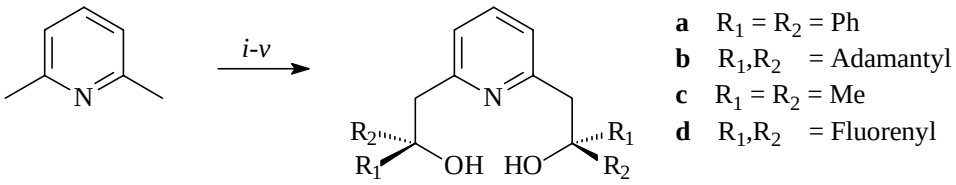
2.1 Introduction.

C_2-symmetrical pyridine diols ligands exemplified in general structure **2.1**, obtained by base induced addition of lutidine **2.2** to ketones, associate with various metals and therefore could be of special interest as complexing agents for the development of new homogeneous catalysts. The combination of two hydroxyl groups and the pyridine nitrogen makes these ligands capable, for example, of stabilizing high-valent osmium alkoxide complexes.[1] With metals like Zr and W good polymerization catalysts are formed.[2] Biomimetic studies of enzymes have been conducted with some Mo complexes.[3] Well defined complexes with Ti,[4] Zn[5], Co[5], Si[6] and Ru[7] have also been reported in literature.



2.1

The synthesis of this class of compounds was first reported by Tilford and Van Campen[8] and further explored by Berg and Holm[3b] in the synthesis of 2,6-bis(2,2-diphenyl-2-hydroxyethyl)-pyridine **2.1a**. These compounds have been of interest in our group as model systems for zinc alcohol dehydrogenase[5b], carboxypeptidase[9] and for preparation of silicon alkoxides.[6a] Several derivatives have been prepared using the described methodology for the synthesis of 2,6-bis(2,2-diphenyl-2-hydroxyethyl)-pyridine **2.1a** (Scheme 2.1). This approach consists of a one-pot, two-step synthesis. Yields are moderate; the benzophenone based pyridine diol **2.1a** is obtained in 35% yield, whereas derivatives based on adamantanone (**2.1b**),[10] acetone (**2.1c**),[5b] and fluorenone (**2.1d**)[5b] are obtained in yields of 51, 34, and 13%, respectively.



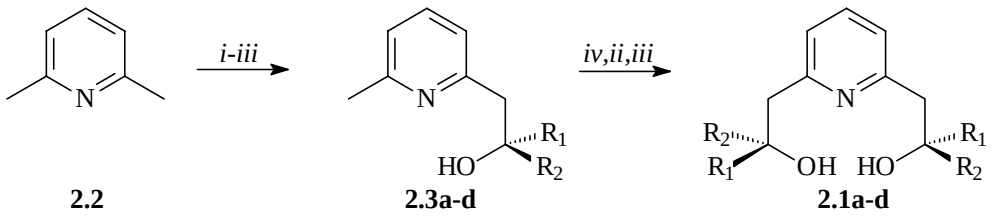
2.2 **2.1a-d**

Scheme 2.1 *Reagents and conditions: i, n*-BuLi (1.1 equiv.), THF, -60 °C; *ii* R_1R_2C=O; *iii n*-BuLi (1.1 equiv.), -80 °C; *iv* R_1R_2C=O; *v* 2N HCl.

2.2 Improved Synthesis of C_2-symmetrical Pyridine Diols.

2.2.1 Pyridine Diol Synthesis Using a Two-Step,Two-Pot Approach and Formation of C_s-symmetrical Pyridine Diols.

Although the previously described approach has been applied for the synthesis of a wide variety of pyridine diols **2.1a-d** the yields are always moderate to low, restricting its general applicability. We found that overall yields could be improved substantially if a two-pot approach was used in which the monoadduct **2.3** is isolated first and converted to the C_2-symmetrical diadduct **2.1** (Scheme 2.2). The monoadducts **2.3** formed by addition of monolithiated lutidine to benzophenone, adamantanone, acetone, and fluorenone can be isolated readily in 85, 88, 75, and 46% yields, respectively. In the second reaction step these monoadducts are converted to the corresponding pyridine diols **2.1a-d** by adding slightly more than two equivalents of base followed by the addition of the ketone.



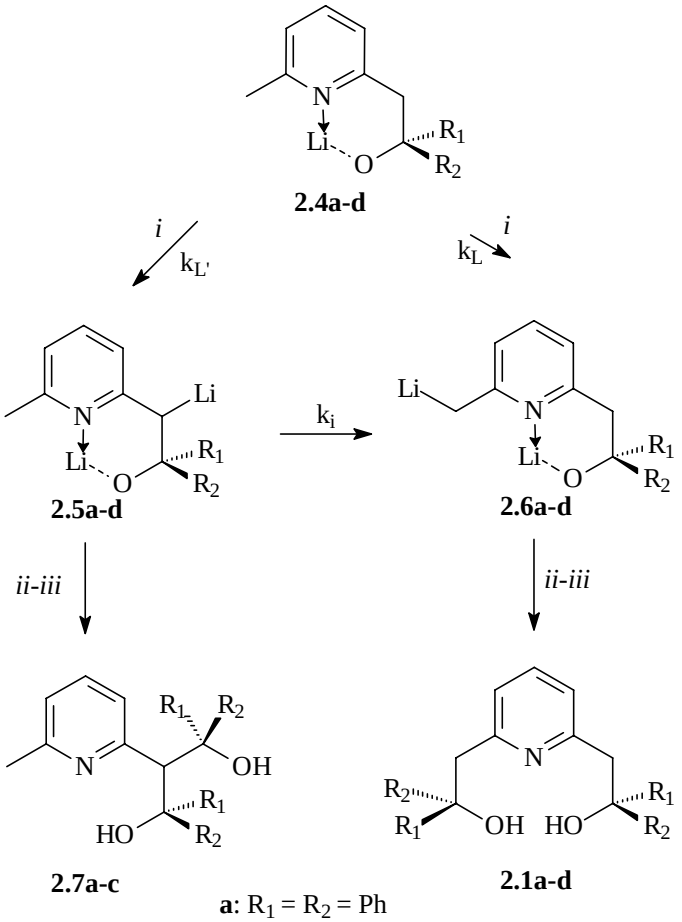
2.2 **2.3a-d** **2.1a-d**

Scheme 2.2 *Reagents and conditions: i, n*-BuLi (1.1 equiv.), THF, -60 °C; *ii* $R_1R_2C=O$; *iii* 2N HCl; *iv n*-BuLi (2.1 equiv.), THF, rt.

The second reaction step, however, is less straightforward than it appears. The time span after lithiation and before addition of the ketone (effective lithiation time) strongly influences the yield of the desired C_2-symmetrical product **2.1**. Using this two-pot synthetic approach, it was found that if a lithiation time of 4 hours was applied for the adamantanone derivative **2.3b**, after which one equivalent of adamantanone was added, followed by work up with 2N HCl, the adamantanone based C_2-symmetrical pyridine diol **2.1b** could be isolated in 70% yield (overall yield 62%). However, when adamantanone was added after a lithiation time of only 30 min, a second product, C_s-symmetrical pyridine diol **2.7b**, was also isolated. The formation of **2.7b** must involve deprotonation of the CH_2-group forming the dilithiated intermediate **2.5b** instead of deprotonation at the presumably less sterically hindered methyl group, which gives rise to the intermediate **2.6b** (Scheme 2.3).

Some experiments at different temperatures and with different lithiation times were conducted in order to obtain further mechanistic insight. In these experiments, monosubstitution product **2.3b** was treated with two equivalents of *n*-butyllithium under the given conditions. The ratios of the C_s-symmetrical adduct **2.7b** and C_2-symmetrical adduct **2.1b** were determined by means of the integration of the signals in the ^{1}H NMR after quenching the reaction with adamantanone and workup with 2N HCl.

The results are given in Table 2.1. T_1 is the effective lithiation time namely the time between the addition of *n*-butyllithium and the addition of the adamantanone. T_2 is the time the mixture is stirred after the addition of the ketone and before it is quenched with HCl.



Scheme 2.3 *Reagents and conditions: i, n*-BuLi (1.1 equiv.), THF; *ii* adamantanone; *iii* 2N HCl.

At –80°C lithiation is slow (entries 1 and 2) and even at –40°C complete lithiation requires several hours to go to completion (entries 3 through 5). Lithiation is clearly far more rapid at 0°C and there is a clear tendency with short lithiation times for **2.7b** to predominate over **2.1b** although the ratio clearly tends towards the latter at longer lithiation times (entries 6 through 9). This trend is even clearer at room temperature; fairly long lithiation times lead to a striking reversal of the ratio **2.7b** over **2.1b** (entries 10 through 14).

Table 2.1: *Dependence of the formation of **2.1b** and **2.7b** on the lithiation conditions.*

Entry	Reaction Temp. [°C]	T_1	T_2	Yield of **2.7b**	Yield of **2.1b**
1.	- 80	5 min	4 h	-	-
2.	- 80	4 h	4 h	34.4	35.6
3.	- 40	10 min	90 min	18.5	20.4
4.	- 40	30 min	90 min	19.1	23.9
5.	- 40	60 min	90 min	20.6	34.3
6.	0	¾ min	60 min	61.7	16.3
7.	0	5 min	60 min	61.0	29.5
8.	0	30 min	60 min	60.4	38.5
9.	0	60 min	60 min	58.3	41.5
10.	r.t.	½ min	60 min	66.4	14.5
11.	r.t.	5 min	60 min	63.0	37.0
12.	r.t.	30 min	60 min	54.5	45.5
13.	r.t.	60 min	60 min	28.6	71.4
14.	r.t.	4 h	60 min	4.8	95.2

From these results it seems justified to conclude that the lithium alkoxide first formed (**2.4b**) is deprotonated at the CH_2-group (**2.5b**) more rapidly than at the methyl group (**2.6b**). In other words $k_{L'} > k_L$. This effect is assumed to arise from coordination of the second equivalent of *n*-butyllithium to the electron rich oxygen in the chelate ring of **2.4b,** followed by facile intermolecular deprotonation at the CH_2-group as shown in Fig. 2.1. A second conclusion is that **2.6b** is thermodynamically more stable than **2.5b**. Whether the slow conversion of **2.5b** to **2.6b** is due to inter- or intramolecular processes cannot be concluded from the data of Table 2.1.

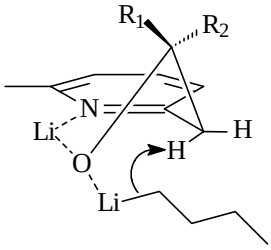
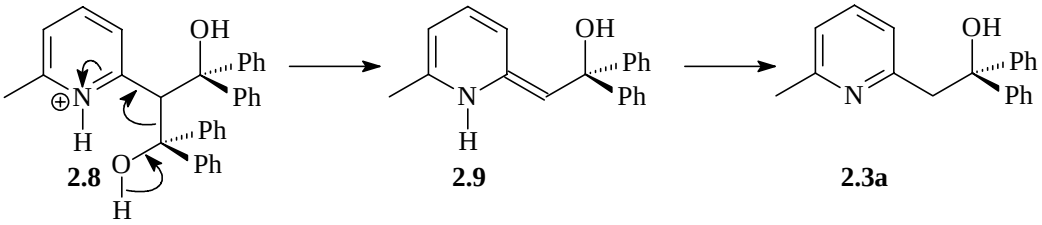


Figure 2.1 *Six-membered intermediate.*

Using the data of Table 2.1 as guide, the reaction conditions were optimized for formation of the C_s-diol **2.7b**. This entailed lithiation and quenching at room temperature after a lithiation time of 30 sec. whereby the product was obtained in 52% yield.

When similar temperature and time dependent lithiation experiments were carried out with the diphenylcarbinol **2.3a,** only C_2-symmetrical diol **2.1a** and some starting materials in the reaction mixture were detected. However, when longer lithiation times at room temperature were used starting material was still recovered despite the fact that lithiation at this temperature and with these lithiation times should be complete. It was also observed that

the yield of the C_2-symmetrical diol **2.1a** increased on prolonged lithiation times. These observations are consistent with the formation of intermediate **2.5a** even though no trace of the C_s–adduct **2.7a** was detected. However, on modification of the workup procedure the C_s-symmetrical diol **2.7a** was obtained. When 2N NH_4Cl was used in the workup the C_s-symmetrical diol **2.7a** could be isolated in moderate to low yield (5-35%) depending on the reaction conditions (-80°C to RT). The usual workup with 2N HCl is too acidic to keep the diol **2.7a** intact. Experiments with various lithiation times and at different temperatures followed by workup with 2N NH_4Cl showed the same phenomenon as observed for the adamantanone adduct. Initially, lithiation of the alkoxide **2.4a** is preferred at the CH_2-group forming dilithio species **2.5a,** which is converted to **2.6a** on prolonged lithiation times.



Scheme 2.4 *Retro addition.*

When the C_s-diol **2.7a** was stirred with 2N HCl it indeed reverted to the mono benzophenone adduct **2.3a** and benzophenone (Scheme 2.4). This retro addition is probably initiated by protonation of the pyridine nitrogen of **2.8,** followed by expulsion of the benzophenone moiety affording intermediate **2.9,** which finally rearranges to the pyridine.

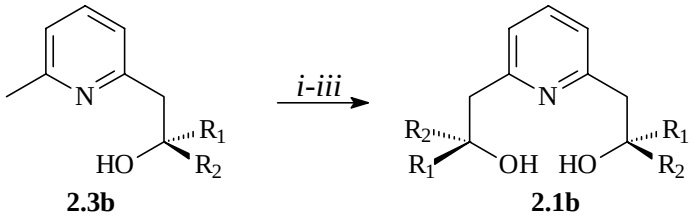
The retro addition can also be induced by sonication or heat.[11] Retro addition also occurs upon purification of the product by means of column chromatography on silica. The retro addition is also observed for the C_s-diol **2.7b** under acidic conditions at higher temperatures. The best conditions for the formation of the C_s-diol **2.7a** were found at 0°C with a lithiation time of 1 min giving the product **2.7a** in 35% yield. The optimal conditions for the formation of the C_2-diol **2.1a** involve a lithiation time of 4h at r.t. to afford **2.1a** in 67% yield. For the acetone derivative the C_s-diols also were observed in 5-10% yield. No efforts were made to improve the yield of this product. In case of the fluorenone adducts it was not possible to isolate the C_s-diols.

Previous investigations of addition of the CH_2-group of this type of compounds to carbonyl functionalities did not lead to report of the formation of the C_s-diols.[3a,5b,6a,12] The observation that in most cases only low to moderate yields are obtained of the C_2-diol **2.1** and the fact that starting materials are recovered are consistent with lithiation and addition having occurred at the CH_2-group. The products, however, were probably not stable enough to isolate. We conclude that addition reaction at this position can and does take place and that in some cases the C_s-symmetrical diols **2.7** can be isolated provided that they are sufficiently

stable to survive retro addition. The almost exclusive synthesis of the C_2-diols **2.1** as a single product using this approach appears possible, though long lithiation times are required ensuring that all kinetic product is converted into the thermodynamic product, which is possible with a reaction time of at least 4 hours.

2.2.2 Exclusion of C_s-symmetrical Pyridine Diols using KDA.

Since exclusive synthesis of the C_2-diols **2.1** would require long reaction times a different approach was developed making use of the understanding of the reaction course that was gained in conducting the time dependent lithiations. If a base is used that leads less readily to the six-membered intermediate chelate (Fig. 2.1) the deprotonation at the CH_2-group should not be kinetically favored and deprotonation should only take place at the less hindered methyl group. When the adamantanone alcohol **2.3b** was deprotonated with 2.1 equivalents of potassium diisopropylamide (KDA) and quenched with adamantanone after only 15 min of stirring, the C_2-diol **2.1b** was obtained as sole product in 95 % yield (Scheme 2.5). KDA is a very strong base and the potassium does not strongly coordinate with the nitrogen and the oxygen. After deprotonation of the hydroxyl group, the second attack apparently occurs at the sterically less hindered methyl group and no reaction at the CH_2-group is observed. Not only is this approach very selective but it also provides the C_2-diols after stirring for a short time.



2.3b **2.1b**

Scheme 2.5 *Reagents and conditions: i,* KDA (2.1 equiv.), THF, -50 °C; *ii* $R_1R_2C=O$; *iii* 2N NH_4Cl.

When this new approach was also applied in the synthesis of the benzophenone based C_2-diols **2.1a, 2.1c** and **2.1d** the products were isolated in high yields (Table 2.2).

A second effect caused by the potassium was found when C_s-diol **2.7b** was deprotonated with two equivalents of KDA and allowed to stir overnight. Retro addition of a large amount of the starting material was observed (70%), 25 % of the starting material was recovered and to a small extent the C_2-diol **2.1b** was isolated (5%). Retro addition under these conditions, however, is slow and the contribution of this pathway in the formation of the C_2-diols **2.1** from the pyridine alcohols **2.3** therefore is small. The formation of the C_2-diol reveals that after retro addition the methyl group is deprotonated and reacts with the

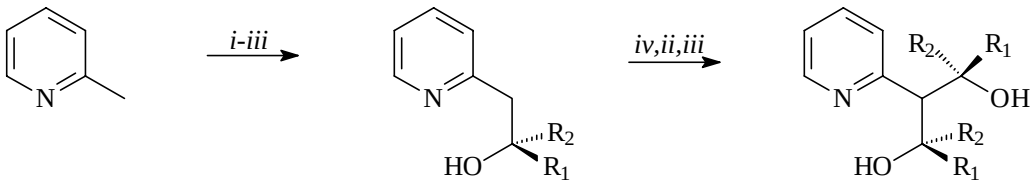
adamantanone which is formed during the retro addition. The low yield of the C_2-diol could be caused by a slow potassium shift from the CH_2-group to the methyl.

Table 2.2: *Summery of optimized yields for the synthesis of C_2- diols **2.1**.*

used ketone	Mono adduct **2.3** (yield using *n*-BuLi)	bis adduct **2.1** (yield using KDA)	overall yield of **2.1**
Benzophenone	**2.3a** (85%)	**2.1a** (90%)	77%
Adamantanone	**2.3b** (88%)	**2.1b** (95%)	84%
Acetone	**2.3c** (75%)	**2.1c** (71%)	53%
Fluorenone	**2.3d** (46%)	**2.1d** (75%)	35%

2.3 Selective Synthesis of C_s-symmetrical Pyridine Diols.

The C_s-diols also have interesting features, as they are known to coordinate various metals,[13] and it would be desirable to have a synthetic approach that would selectively afford the C_s-diols. In our hands it was not possible to synthesize the lutidine based C_s-diols as a single product without the formation of the thermodynamically more stable C_2-diols. Since lithiation at the methyl group is thermodynamically favored over lithiation at the CH_2-position and since conversion of the kinetic product to the thermodynamically product occurs, it will be very difficult to synthesize the C_s-diols as single product using this approach. This problem is readily circumvented by use of 2-picoline **2.10**, which when deprotonated with *n*-butyllithium and quenched with benzophenone, adamantanone, acetone or camphor provides pyridine alcohols **2.11** in good yields. The isolated pyridine alcohols **2.11** were subsequently lithiated with two equivalents of *n*-butyllithium and allowed to react with a second ketone in order to give the desired C_s-diol **2.12**. For the benzophenone, adamantanone and acetone adducts the C_s-diols **2.12a, 2.12b** and **2.12c** indeed were found in 33, 26 and 30% isolated yields, respectively (Scheme 2.6).



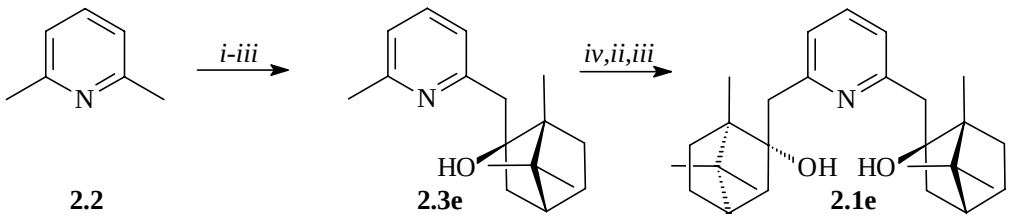
2.10 **2.11a-d** **2.12a-b**

Scheme 2.6 *Reagents and conditions: i, n*-BuLi (1.1 equiv.), THF, -60 °C; *ii* R_1R_2C=O; *iii* 2N NH_4Cl; *iv n*-BuLi (2.1 equiv.), THF.

The diols **2.12a** and **2.12b** undergo retro addition to the pyridine alcohol **2.11** and the ketones under acidic conditions or elevated temperatures making purification of the compounds very difficult. The diol **2.12c** is more stable and retro addition occurs only above 100°C or under highly acidic conditions. When pyridine alcohol **2.11d** was used for the preparation of the C_s-diol no diol was observed and only starting materials were recovered.

2.4 Chiral Non-racemic Camphor Based Pyridine Alcohols.

So far only the use of achiral symmetrical ketones has been described for the synthesis of achiral pyridine alcohols. The following step is the synthesis of chiral nonracemic pyridine alcohols that might be used for catalytic asymmetric synthesis. In order to obtain chiral pyridine alcohols prochiral (mirror image faces) ketones or chiral ketones have to be used. Addition of lutidine to prochiral ketones gives a racemic mixture that must be resolved in order to obtain optically active pyridine alcohols. Facially selective addition to prochiral ketones would give chiral-nonracemic pyridine alcohols, but a chiral additive is required and there is no guarantee that facial selection would be absolute. Facially selective addition to chiral ketones would afford chiral nonracemic pyridine alcohols in just one step without any other chiral additive. Of all ketones from the chiral pool camphor (the (+) as well as the (-) enantiomer) is one of the cheapest and best studied ketones for selective addition. Since Noyori has applied (-)-dimethylamino isoborneol as highly effective catalyst for the enantioselective addition of diethylzinc to aldehydes the compounds possessing a camphor skeleton have been an object of increasing interest.[14] Camphor commonly reacts nearly exclusively from the *endo* side since the *exo* side is blocked by the methyl groups.[15,16] We therefor decided to investigate the addition of 2,6-lutidine **2.2** to camphor. When 2,6-lutidine **2.2** was deprotonated with *n*-butyllithium at –60° and allowed to react with (*R*)-(+)-camphor indeed an *endo* selective addition to the ketone was observed. The pyridine alcohol **2.3e** was isolated in 90% yield (Scheme 2.7).

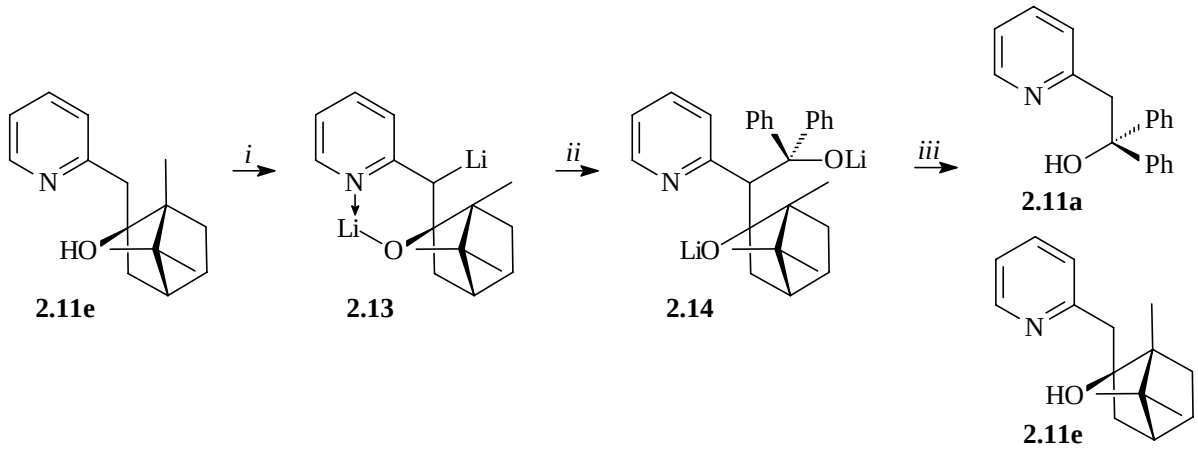


2.2 **2.3e** **2.1e**

Scheme 2.7 *Reagents and conditions: i*, *n*-BuLi (1.1 equiv.), THF, -60 °C; *ii* (*R*)-camphor; *iii* 2N NH_4Cl, *iv n*-BuLi (2.1 equiv.), THF, -40 °C.

When the time and temperature dependent lithiation was carried out for the camphor adduct **2.3e**, again an increase in the formation of the camphor based C_2-diol **2.1e** upon

longer lithiation times was observed. Recovery of starting material at room temperature, however, was substantial (up to 30%). The C_s-diol **2.7e,** however, could not be detected, even when a mild workup procedure was applied. This diol adduct probably is too unstable to be isolated. The fact that double addition can take place at one methyl group is established in an experiment where the 2-picoline based camphor alcohol **2.11e** (obtained from addition of 2-picoline to (*R*)-camphor) is dilithiated to species **2.13** and quenched with benzophenone leading to the mixed adduct **2.14**. This product, however, is also very unstable and upon workup the starting camphor based alcohol **2.11e** was isolated together with a reasonable amount (40%) of benzophenone based alcohol **2.11a**. Addition at the CH_2-group does take place, but the mixed adduct formed is too unstable to be isolated and a retro addition takes place providing either the starting material **2.11e** or the benzophenone adduct **2.11a** (Scheme 2.8).



Scheme 2.8 *Reagents and conditions: i, n*-BuLi (2.1 equiv.), THF, -60 °C; *ii* benzophenone; *iii* 2N NH_4Cl.

The best preparative results for the C_2-diol **2.1e** using the initial approach were at –40°C since at higher temperatures more side products were obtained (Scheme 2.7). When pyridine alcohol **2.1e** was prepared from **2.3e** according the previously described method using KDA as base the pyridine alcohol was obtained in 95% yield. Again complete *endo*-selective addition to camphor was observed. By good fortune we were able to grow suitable crystals for X-ray determination and the *endo* facial selectivity could be established by crystallographic means (Figure 2.2). The molecular structure of **2.1d** in solid state shows an open conformation and the ligand is not completely symmetrical. The small distortion from the C_2-symmetrical geometry is probably due to crystal packing since in the ^1H NMR in $CDCl_3$ no distinction can be made between the two camphor moieties or between the benzylic protons. The nitrogen forms strong intramolecular hydrogen bonds with the hydroxyl groups of the camphor moiety (H(61)…N(1) = 2.02(4), O(1)…H(61) = 0.84(4), H(62)…N(1) = 2.11(4), O(2)…H(62) = 0.79(4)°) and is in this arrangement preorganized for complexation.

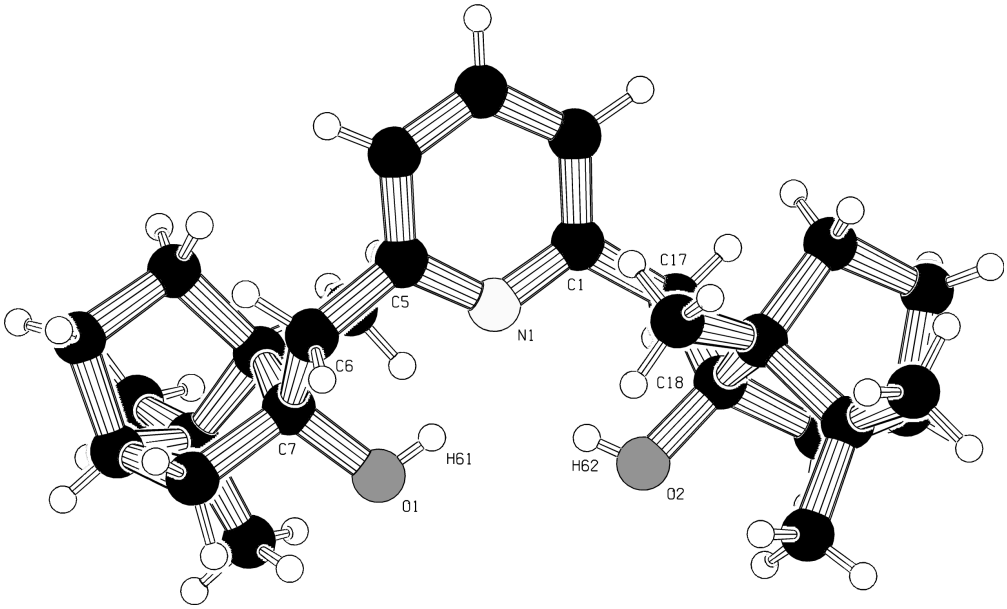


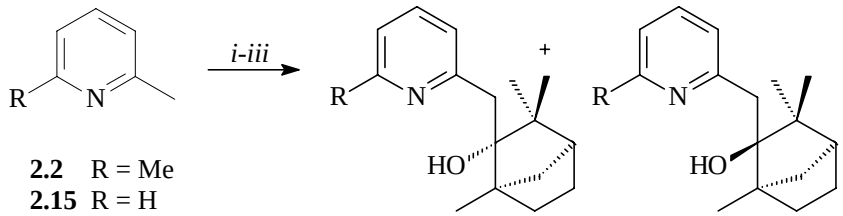
Figure 2.2 *X-ray structure of* ***2.1e****.*

2.5 Regioselective Additions to Other Chiral Ketones.

2.5.1 Facially Selective Additions to Fenchone.

The naturally occurring (*R*)-fenchone has also been used as chiral ketone for facially selective additions. The accessibility of the two diastereotopic faces of the carbonyl group, however, is not as differentiated as for camphor. Examples of *exo*-specific addition are known.[15b,17] In other cases, however, addition is not specific and mixtures of *endo* and *exo* isomers are obtained.[15a,17b,18]

Efforts to add the 2,6-lutidine **2.2** facial selectively to (*R*)-fenchone were less successful. Addition afforded inseparable *exo* and *endo* adducts **2.3f** in equal amounts (Scheme 2.9).



2.2 R = Me
2.15 R = H

endo-2.3f R = Me **exo-2.3f** R = Me
endo-2.11f R = H **exo-2.11f** R = H

Scheme 2.9 *Reagents and conditions: i, n*-BuLi (1.1 equiv.), THF, -60 °C; *ii* (*R*)-fenchone; *iii* 2N NH_4Cl.

Addition of 2-picoline **2.15** to (*R*)-fenchone also afforded a mixture of *exo* and *endo* enantiomers **2.11f** in 3:2 ration. The *exo* isomer, however, could be crystallized selectively from hexane, and an enriched mixture of *endo* and *exo* isomers remains in the solution.

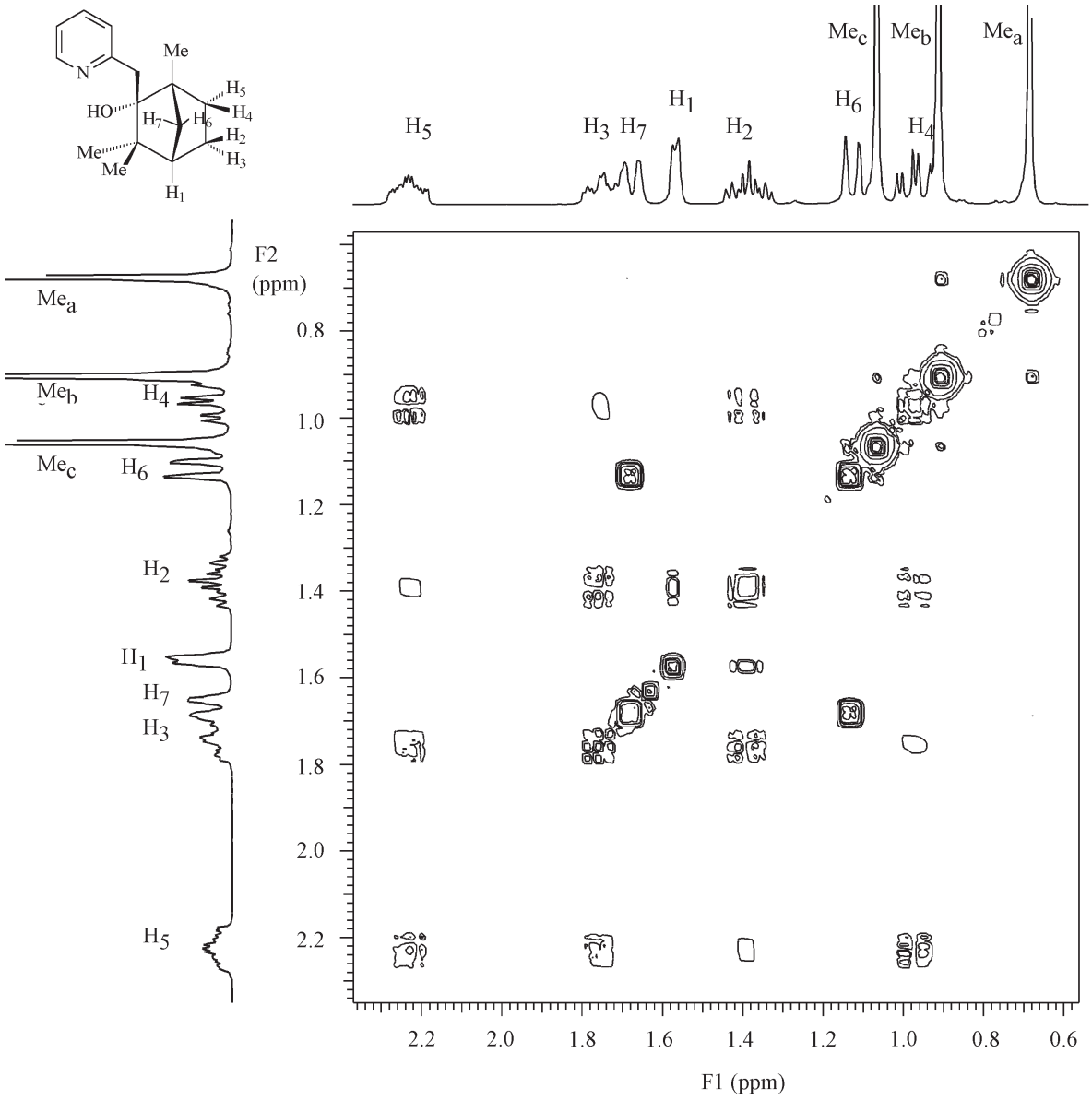


Figure 2.3 *COSY spectrum of exo-**2.11f**.*

The configuration of the isomers was assigned by means of *HETCOR*, *COSY* and *NOESY* experiments. From *HETCOR* (not shown) the signal at δ 1.58 was assigned as H_1. Furthermore three set of signals for the three CH_2-groups of the fenchone moiety are found (δ 0.98 and 2.25; δ 1.77 and 1.40; and δ 1.70 and 1.14).

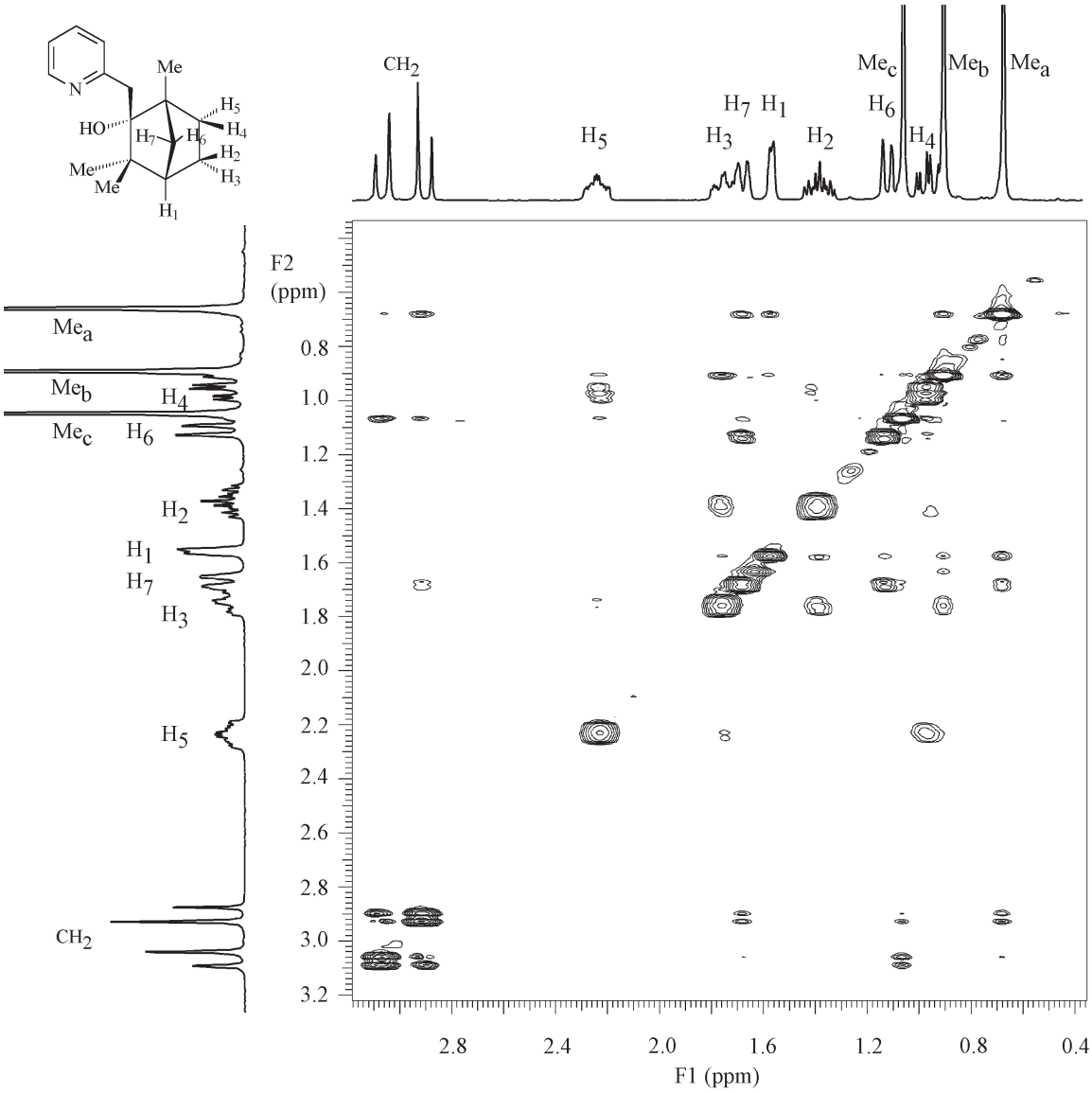
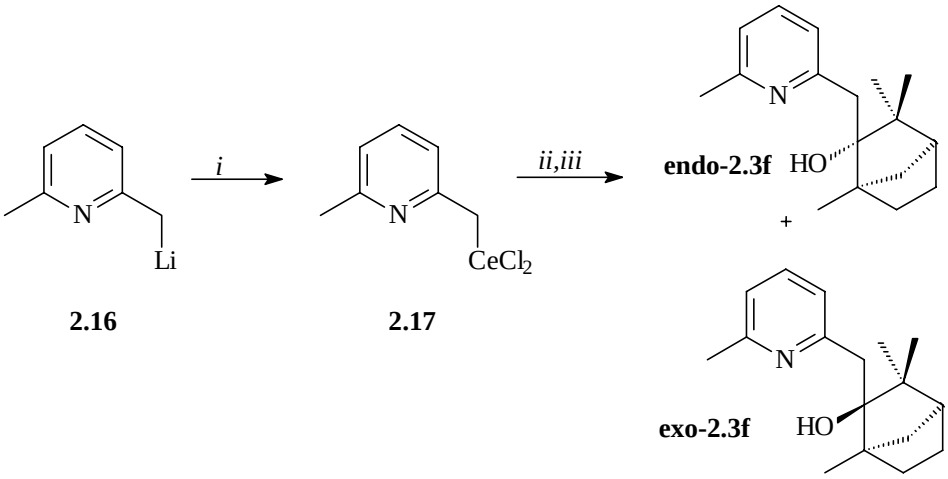


Figure 2.4 *NOESY spectrum of exo-**2.11f**.*

In the *COSY* NMR (Figure 2.3) signals at δ 1.70 and 1.14 show no correlation with any of the other protons and therefore are assigned as H_6 and H_7. The signal at δ 1.70 furthermore shows a clear *NOE* interaction with Me(a) at δ 0.70 indicating that this signal arises from H_7 (Figure 2.4). The signal at δ 1.14 therefore belongs to H_6. Me(a) has a *COSY* correlation with Me(b) at δ 0.91, therefore the signal at δ 1.08 belongs to Me(c). H_1 at δ 1.58 has a *COSY* interaction with the signal at δ 1.40 indicating that this signal and the signal at δ 1.77 belong to the neighboring protons H_2 and H_3. The signal at δ 1.40 itself shows a *NOE* with H_6 and therefore is assigned as H_2, subsequently the signal at δ 1.77 must be from to H_3. H_3 has a *COSY* correlation as well as a *NOE* interaction with the signal at δ 2.25, whereas H_2 has a *COSY* and *NOE* interaction with the signal at δ 0.98. Thus H_4 correlates with the signal

at δ 0.98 and H_5 correlates with the signal at δ 2.25. This is confirmed by the *NOE* interaction of H_4 with H_6 and by the *NOE* interaction of H_5 with Me(b).

Since the separation of isomers is only possible for the 2-picoline based product **2.11f** experiments to improve the facial selectivity were conducted. It was found that higher isomeric ratios with the fenchone derivative could be obtained when the lithium in the monolithio species **2.16** was replaced by $CeCl_2$ (addition of $CeCl_3$·THF[19] subsequently to lithiation), followed by the addition of (*R*)-fenchone. Alkylcerium reagents are known to give clean 1,2-addition to 'difficult' ketones.[20] This is presumed to be due to the reduced basicity and the oxaphilicity of the cerium alkyl reagent.[21] Furthermore complexation of the cerium to the carbonyl functionality and subsequent attack of the alkyl group at the carbon atom enhances selectivity. We thought that complexation of the alkylcerium reagent to the carbonyl could improve the regioselectivity of the addition reaction to fenchone.



2.16 **2.17**

Scheme 2.10 *Reagents and conditions: i,* $CeCl_3$·THF, -70 °C; *ii* (*R*)-fenchone; *iii* 2N NH_4Cl.

Indeed some improvement was found when the cerium species **2.17** was synthesized in situ from the lithio species **2.16** and allowed to react with (*R*)-fenchone. However, a mixture of the two isomers of **2.3f** was still obtained although the *endo*/*exo* isomer ratio for this reaction improved to 1:2 at –50°C in THF. When the reaction temperature was lowered to –80°C a small improvement of the ratio to 1:4 was found (Scheme 2.10).

2.5.2 Facially Selective Addition to Menthone.

Addition of the lithio species **2.16** to (-)-menthone gave a mixture of the *cis* and *trans* isomers **2.3g** in a ratio of 16:5 in favor of the *cis* adduct (Scheme 2.11). These isomers could be separated by means of column chromatography. The configurations of the isomers were deduced from the *HETCOR*, *COSY* and *NOESY* NMR spectral data. The *HETCOR* experiment on the minor adduct (not shown) led to the conclusion that the signals at δ 2.44,

1.37 and 1.33 ppm were from the CH-groups.[22] The signal at δ 2.44 exhibits a *COSY* interaction (Figure 2.5) with Me(b) and Me(c) and is therefore assigned as H_f. A *COSY* interaction of H_f with the signal at δ 1.33 indicates that this signal belongs to H_a.

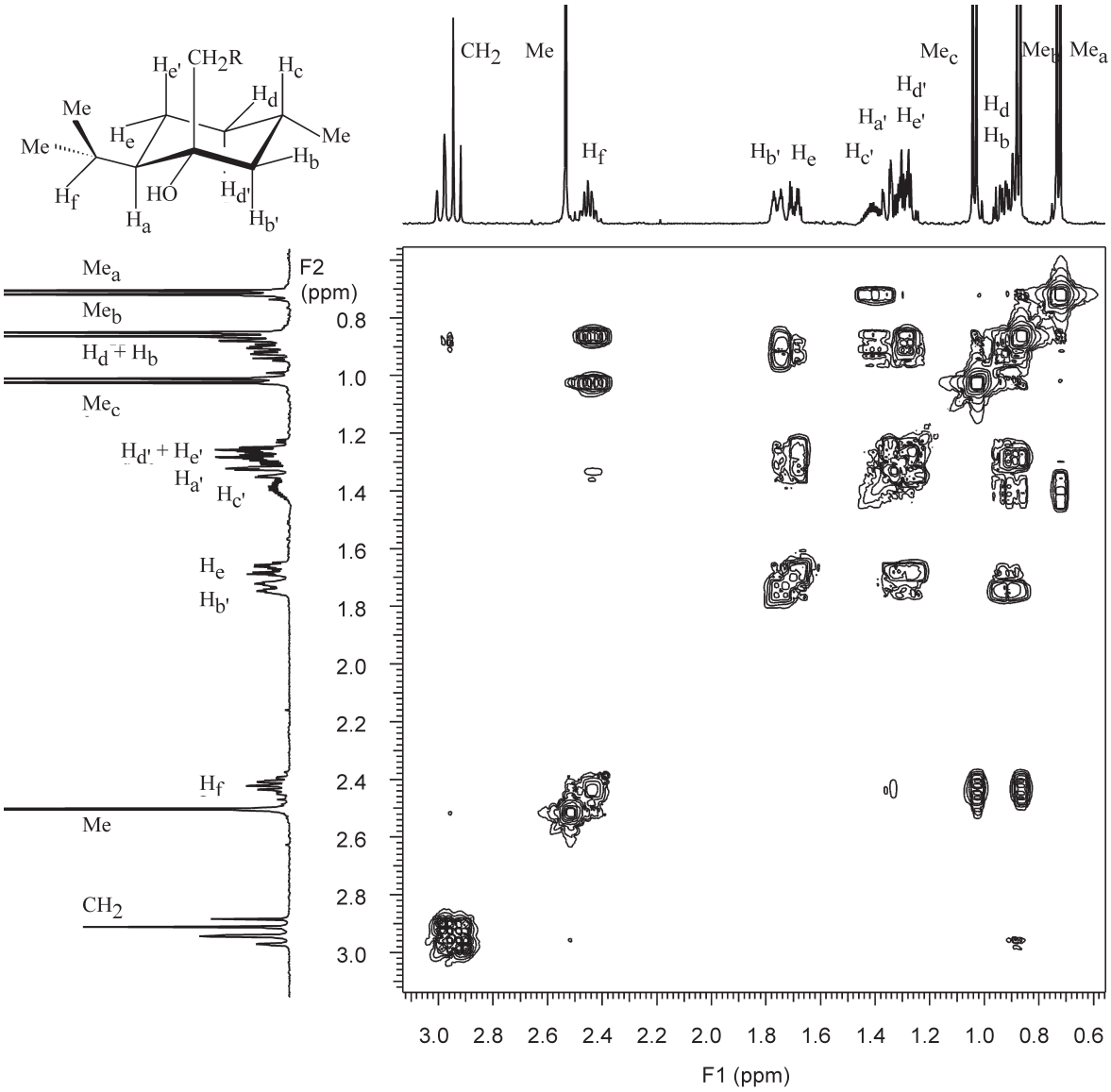


Figure 2.5 *COSY spectrum of trans-**2.3g**.*

The signal at 1.37 therefore can only belong to H_c, which is confirmed by the *NOE* (Figure 2.6) and *COSY* interactions with Me(a). The benzylic CH_2-group in this minor isomer was found to have a *NOE* interaction with H_c, Me(b), H_f and with one other axial proton ($H_{e'}$).[23] Therefore the minor product was assigned as the product *trans*-**2.3g**. The *NOESY* spectrum (not shown) of the major product clearly shows a *NOE* interaction of the equatorial benzylic CH_2-protons with the proton H_f and the axial proton H_a indicating that this is the product *cis*-**2.3g**.

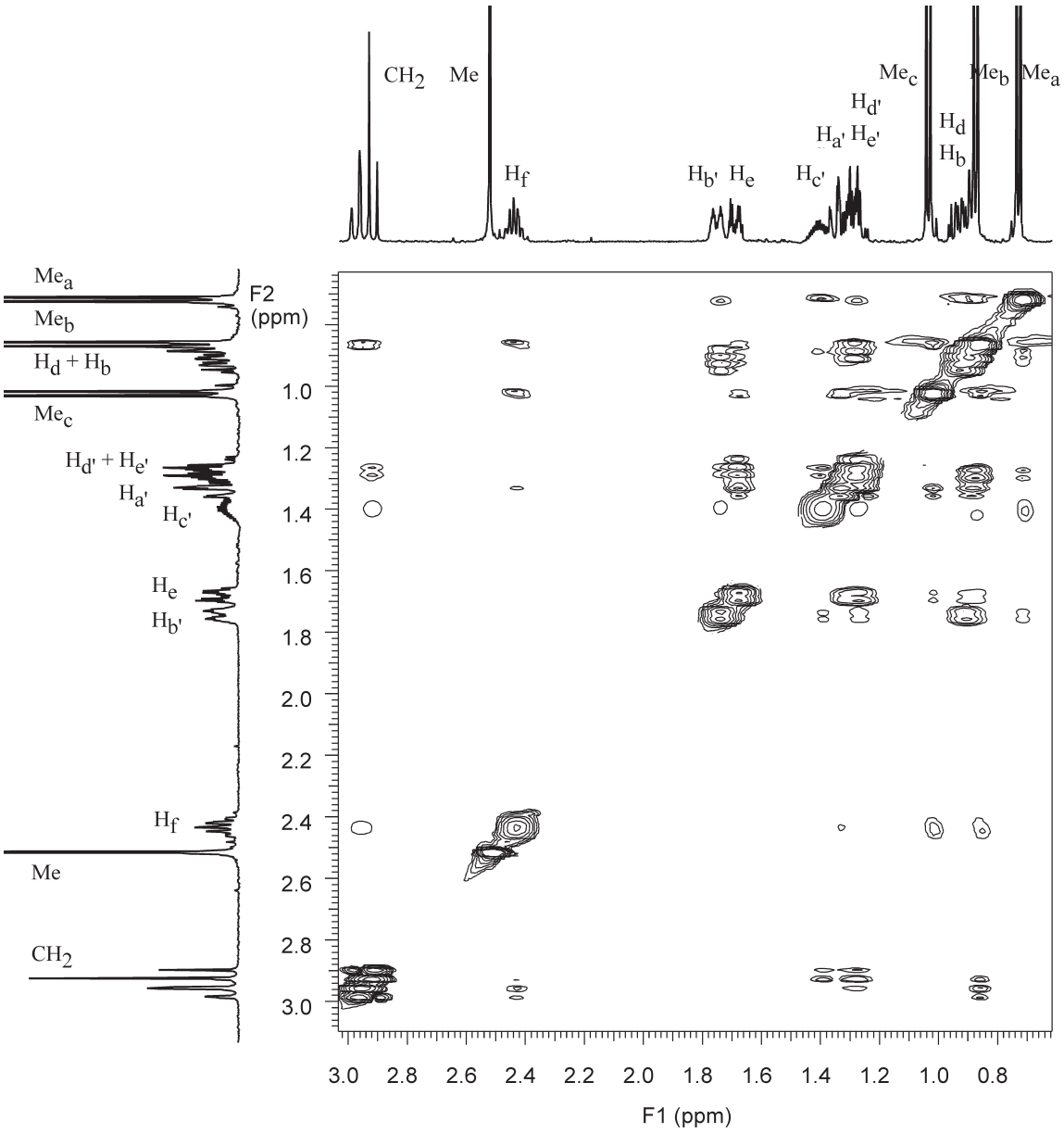
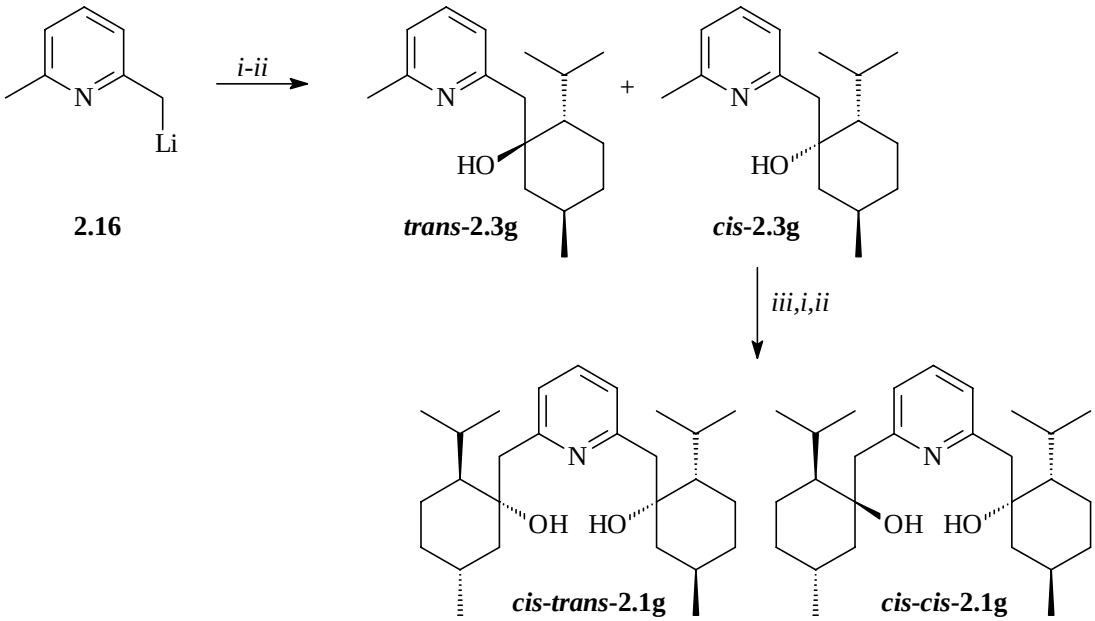


Figure 2.6 *NOESY spectrum of trans-**2.3g**.*

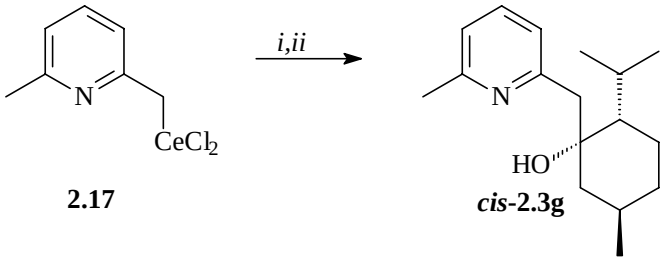
When the *cis*-**2.3g** isomer was lithiated with two equivalents of *n*-butyllithium and allowed to react with (-)-menthone the bisproduct was formed as a mixture of the isomers *cis-cis*-**2.1g** and *cis-trans*-**2.1g** in a ratio of 6:1 (Scheme 2.11). The *cis-cis*-**2.1g** isomer could be isolated as a pure product by selective crystallization from a mixture of water/ethanol.



2.16 ***trans*-2.3g** ***cis*-2.3g**

Scheme 2.11 *Reagents and conditions: i,* (-)-menthone, -60 °C; *ii* 2N NH_4Cl; *iii n*-BuLi (2.1 equiv.), THF, 0°C.

Addition of the cerium alkyl species **2.17** to (-)-menthone led to far better results. When menthone was allowed to react with **2.17** at –80°C only the *cis*-isomer **2.3g** was formed (Scheme 2.12).



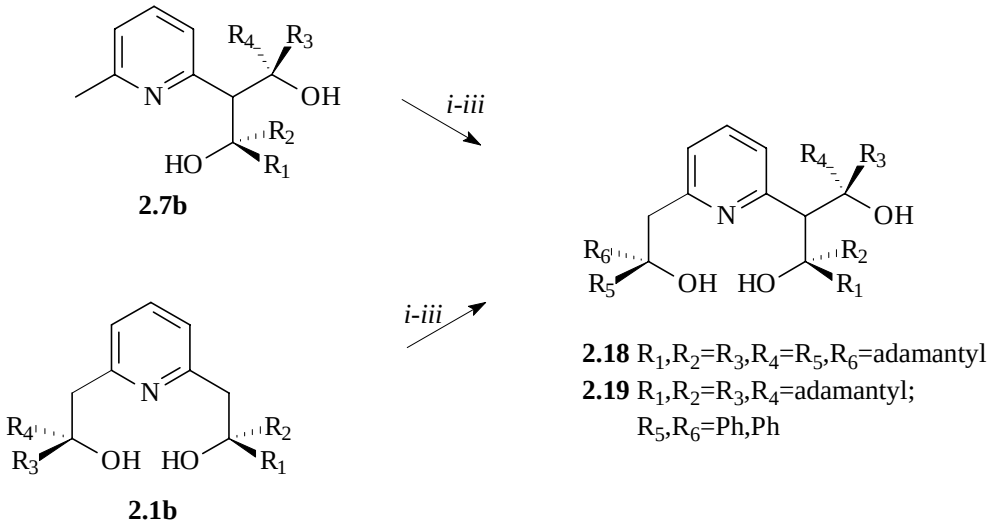
2.17 ***cis*-2.3g**

Scheme 2.12 *Reagents and conditions: i,* (-)-menthone, -70 °C; *ii* 2N NH_4Cl.

2.6 Pyridine Triols.

Thus far research has focussed on the synthesis of pyridine diols and mono alcohols. It would be interesting to see whether it is possible to generate pyridine triols and tetraols. To synthesize pyridine triols two possible pathways can be taken. Starting from the C_s-diol lithiation at the methyl group is required. Starting from the C_2-diol lithiation at a more sterically hindered CH_2-group is required. When C_s-diol **2.7b** was lithiated with *n*-butyllithium and quenched with adamantanone the triol **2.18b** was obtained in only 10% yield according to ^{1}H-NMR experiments. When C_2-diol **2.1b** was lithiated with *n*-butyllithium and quenched with adamantanone the triol **2.18** was obtained in only 5% yield (Scheme 2.13).

Deprotonation of the methyl or CH_2-group of these diols is slow and does not provide highly reactive nucleophiles. When diol **2.7b** was deprotonated with *n*-butyllithium and quenched with benzophenone, which is a more reactive ketone compared to adamantanone, we obtained the triol **2.19** in 35% yield. The use of a stronger base like KDA is not possible since this base gives rise to retro addition. In view of the difficulties in synthesizing the pyridine triols no experiments were conducted to synthesize the tetraols.



Scheme 2.13 *Reagents and conditions: i,* *n*-BuLi (3.5 equiv.), THF, 0°C; *ii* $R_5R_6C=O$; *iii* 2N NH_4Cl.

2.7 Conclusions.

Aided by the understanding of the lithiation process an approach has been developed that allows the preparation of chiral as well as achiral C_2-symmetrical pyridine diols **2.1** in high yields. The synthetic approach to C_s-symmetrical pyridine diols **2.7** and **2.12** opens up a route to interesting new ligands the complexation behavior of which is currently under investigation. The use of $CeCl_3$·THF[19] in the addition reaction of 2,6-lutidine to menthone gave a regiospecific addition to the pyridine diol ***cis*-2.3g**. Application of $CeCl_3$·THF in the addition reactions opens up a new perspective for regioselective addition to chiral ketones, as shown for menthone. The synthesis of pyridine triols was accomplished starting either from the C_s-diol **2.7b** or the C_2-diol **2.1b**. Best results were obtained with the more reactive benzophenone.

2.8 Experimental Section.

General Remarks: All reactions were carried out under an Ar atmosphere. The following solvents were distilled prior to use: THF, diethyl ether and toluene were distilled from Na wire, acetonitrile was distilled over CaH_2, and dichloromethane, ethyl acetate, and hexane

were distilled over P_2O_5. Column chromatography was performed on alumina (Merck 90, II/III, 0.063-0.200 mm) or silica gel (Aldrich 60, 230-400 mesh). Elemental microanalyses were carried out in the analytical department of this laboratory. X-ray diffraction studies were carried out in the Crystal Structure Center of this laboratory. ^{1}H and ^{13}C spectra were recorded using a Varian Unity Plus Varian 500, a Varian VXR 300 instrument or a Genuine 200 Instrument. The chemical shifts are expressed relative to $CDCl_3$ for ^{1}H NMR (at δ 7.26 ppm) and ^{13}C NMR (at δ 76.91 ppm). *NOESY*,[24] and *COSY*[25] spectra were performed using standard Varian pulse programs. Deuterated solvents were dried over an Al_2O_3 (activity 1) column just prior to use. Melting points (uncorrected) were determinated on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope. IR spectra were recorded from KBr pallets on a Mattson-4020 Galaxy FT-IR spectrophotometer. Reagents and starting materials used were obtained from Aldrich, Fluka or Acros Chimica and used as received, unless noted otherwise.

2-(6-Methyl-2-pyridinyl)-1,1-diphenyl-1-ethanol 2.3a

2,6-Lutidine **2.2** (10.0 g, 93.3 mmol) was dissolved in 200 mL of THF and cooled to –60°C. *n*-Butyllithium (1.6 M in hexane, 59.4 mL, 95.0 mmol) was added under stirring. The mixture was warmed to –50°C and stirring was continued for 1 h before benzophenone (17.3 g, 95.6 mmol) in 25 mL of THF was added by means of canula. The mixture was allowed to reach ambient temperature overnight and was acidified to pH 1 with 2 N HCl. After stirring for 1 h, the mixture was neutralized with 2N NaOH. The aqueous layer was extracted with ethyl acetate twice and the organic layers were dried over $MgSO_4$. After concentration in vacuo the product was recrystallized from methanol yielding a colorless solid (23.0 g, 79.5 mmol, 85%): mp 124-125°C; IR (KBr): 3250, 2900, 1610, 1600, 1450, 1100, 800, 700, 550 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.67 (s, 2H), 6.90 (m, 2H), 7.15 (m, 2H), 7.23 (m, 4H), 7.40 (m, 1H), 7.49 (m, 4H), 8.17 (br, OH), ^{13}C NMR (300 MHz, $CDCl_3$): δ 24.07 (q), 46.68 (t), 78.21 (s), 120.93 (d), 121.43 (d), 126.08 (d), 126.24 (d), 127.74 (d), 136.97 (d), 147.31 (s), 156.73 (s), 158.38 (s). HRMS calcd 289.147 found 289.147 Anal. Calcd for $C_{20}H_{19}NO$: C, 83.03; H, 6.62; N, 4.84. Found C, 83.13; H, 6.47; N, 4.87.

2-[(6-Methyl-2-pyridinyl)methyl]-2-adamantanol 2.3b

2,6-Lutidine **2.2** (3.84 g, 35.8 mmol) was dissolved in 100 mL of THF and cooled to –50°C. Subsequently, *n*-butyllithium (1.6 M in hexane, 22.6 mL, 36.2 mmol) was added and stirring was continued for 30 min. A solution of adamantanone (5.41 g, 36.0 mmol) in 10 mL of THF was added slowly and stirring was continued overnight allowing the mixture to reach r.t. slowly. The solution was quenched with 2N HCl and stirred for 15 min before it was neutralized with 2N NaOH. The solution was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. After being taken to

dryness the product was recrystallized from hexane yielding a colorless solid (8.11 g, 31.5 mmol, 88%): mp 131-132°C; IR (KBr): 3250, 2900, 1610, 1600, 1450, 1000, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.4-2.0 (m, 12H), 2.28 (m, 2H), 2.50 (s, 3H), 3.08 (s, 2H), 6.48 (s, OH), 6.94 (d, *J* = 11.7 Hz, 1H), 6.98 (d, *J* = 11.7 Hz, 1H), 7.49 (dd, *J* = 11.7 Hz, *J* = 11.7 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 24.10 (q), 27.18 (d), 32.61 (t), 34.44 (t), 37.11 (d), 38.28 (t), 43.18 (t), 75.18 (s), 120.76 (d), 121.21 (d), 136.84 (d), 157.20 (s), 158.77 (s); HRMS calcd 257.178, found 257.179. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 78.96; H, 9.05; N, 5.45.

2-Methyl-1-(6-methyl-2-pyridinyl)-2-propanol 2.3c[26]

To a stirred solution of 2,6-lutidine **2.2** (1.57 g, 14.7 mmol) in 100 mL of THF at –50°C was added *n*-butyllithium (1.6 M in hexane, 9.20 mL, 14.7 mmol). The solution was stirred for 15 min and acetone (0.90 g, 15.5 mmol) was added. Stirring remained for another hour and subsequently quenched with 2N NH_4Cl and extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was distilled by means of kugelrohr (70°C, 0.05 mm Hg) yielding a colorless oil (1.81 g, 11.0 mmol, 75 %). ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 6H), 2.43 (s, 3H), 2.78 (s, 2H), 6.1 (br, OH), 6.83 (d, *J* = 7.3 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 7.49 (dd, *J* = 7.7 Hz, *J* = 7.3 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 24.14 (q), 29.33 (q), 48.14 (t), 70.49 (s), 120.84 (d), 121.07 (d), 136.88 (d), 157.03 (s), 159.01 (s);

9-[(6-Methyl-2-pyridinyl)methyl]-9*H*-fluoren-9-ol 2.3d

A solution of 2,6-lutidine **2.2** (0.5 g, 4.6 mmol) in 50 mL of THF was cooled to –60°C. *n*-butyllithium (1.6 M in hexane, 2.9 mL, 4.6 mmol) was added and stirring was continued for 15 min. 9-Fluorenone (0.8 g, 4.6 mmol) in 5 mL of THF was added and stirring continued for 3h. After the addition of 2N NH_4Cl the layers were separated. The water layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was obtained after column chromatography (silica, hexane/ethyl acetate 5:1) as a white solid (0.6 g, 2.1 mmol, 46%): mp 118-119°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.63 (s, 3H), 3.17 (s, 2H), 6.70 (d, *J* = 7.3 Hz, 1H), 6.97 (d, *J* = 7.3 Hz, 2H), 7.12 (t, *J* = 6.6 Hz, 3H), 7.28 (t, *J* = 7.3 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 2H), 7.83 (br, OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 24.23 (q), 45.50 (t), 81.80 (s), 119.67 (d), 121.61 (d), 121.66 (d), 123.66 (d), 127.32 (d), 128.34 (d), 137.23 (d), 138.91 (s), 148.99 (s), 157.02 (s), 158.59 (s).

2-({6-[(2-Hydroxy-2-adamantyl)methyl]-2-pyridinyl}methyl)-2-adamantanol 2.1b with *n*-butyllithium.

The monoadduct **2.3b** (1.1 g, 4.3 mmol) was dissolved in 50 mL of THF and *n*-butyllithium (1.6 M in hexane, 5.6 mL, 9.0 mmol) was added to deprotonate the starting material. The mixture was stirred for 4 h before adamantanone (0.65 g, 4.33 mmol) in 5 mL of THF was added. After stirring for 1h 1N HCl was added and after stirring for 30 min it was neutralized with 2N NaOH. The solution was extracted with dichloromethane twice and the combined organic layers were washed over brine and dried over $MgSO_4$. After removal of the solvent the product was recrystallized from ethanol yielding **2.1b** as colorless needles (1.2 g, 3.0 mmol, 70%): mp 199-200°C; IR (KBr): 3500, 2850, 1610, 1600, 1450, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.4-1.9 (m, 20H), 2.00 (m, 4H), 2.24 (m, 4H), 3.13 (s, 4H), 4.21 (s, 2OH), 7.07 (d, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 27.30 (d), 32.73 (t), 34.59 (t), 37.18 (d), 38.33 (t), 44.56 (t), 75.39 (s), 122.48 (d), 136.84 (d), 158.25 (s); HRMS calcd 407.282, found 407.282. Anal. Calcd for $C_{27}H_{37}NO_2$: C, 79.56; H, 9.15; N, 3.44. Found C, 79.44; H, 9.10; N, 3.48.

Time dependent lithiations for 2.3b.

The monoadduct **2.3b** (2.5 mmol) was dissolved in 50 mL of THF and cooled to the temperature given in Table 1, *n*-butyllithium (1.6 M in hexane, 5.5 mmol) was added and the mixture was stirred for the given time T_1. Subsequently, adamantanone (2.5 mmol) in 5 mL of THF was added. Stirring was continued for the given time T_2 at the given temperature. The mixture was quenched with 2N HCl, stirred for 30 min and neutralized with 2N NaOH. The solution was extracted twice with dichloromethane and dried over $MgSO_4$. The product distribution given in Table 1 was determined by means of ^1H NMR by comparison of the integration of the signals for the methyl and CH group of the C_s-diol with the signal for the CH_2-groups of the C_2-diol.

2-({6-[(2-Hydroxy-2-adamantyl)methyl]-2-pyridinyl}methyl)-2-adamantanol 2.7b

The monoadduct **2.3b** (0.5 g, 2.0 mmol) was dissolved in 50mL of THF and cooled to 0°C. *n*-Butyllithium (1.6 M in hexane, 2.6 mL, 4.2 mmol) was added by syringe and the mixture was stirred for 45 sec. A solution of adamantanone (0.3 g, 2.1 mmol) in 2 mL of THF was added at once. Stirring was continued for 1 h at 0°C and the mixture was quenched with 2N HCl, stirred for 30 min at r.t. and neutralized with 2N NaOH. The solution was extracted twice with dichloromethane and dried over $MgSO_4$ .The product was purified by means of column chromatography (silica, hexane/diethyl ether (9:1)) affording a colorless solid (0.42 g, 1.03 mmol, 52%): mp 194-195°C; IR (KBr):3372, 2931, 2898, 1594, 1572, 1456, 1057, 978 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (s, 2H), 1.21 (d, *J* = 12.2 Hz, 2H), 1.39 (d, *J* = 12.2 Hz, 2H) 1.48 (d, *J* = 9.3 Hz, 2H), 1.60 (m, 2H), 1.67 (m, 4H), 1.77-1.84 (m, 6H), 2.04 (d, *J* = 12.7 Hz, 2H), 2.23 (d, *J* = 12.7 Hz, 2H), 2.40 (m, 4H), 2.55 (s, 3H), 3.93 (s, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.10 (s, 2OH), 7.48 (dd, *J* = 7.8 Hz, *J* = 7.8 Hz, 1H); ^{13}C

NMR (300 MHz, $CDCl_3$): δ 26.54 (q), 26.96 (d), 32.90 (t), 32.96 (t), 34.24 (t), 35.07 (t), 36.75 (d), 37.61 (d), 38.03 (t), 47.90 (q), 80.15 (s), 120.97 (d), 123.56 (d), 136.01 (d), 157.31 (s), 160.84 (s); HRMS calcd 407.282; found 256 (-$C_{10}H_{15}O$), 238 (-$C_{10}H_{17}O_2$). CI(NH3) gave a molecular ion at m/e 408. Anal. Calcd for $C_{27}H_{37}NO_2$: C, 79.37; H, 9.37; N, 3.43. Found C, 79.46; H, 9.28; N, 3.43.

2-[6-(2-Hydroxy-2,2-diphenylethyl)-2-pyridinyl]-1,1-diphenyl-1-ethanol 2.1a with n-butyllithium [27]

A solution of monoadduct **2.3a** (1.0 g, 3.5 mmol) was stirred at 0°C and *n*-butyllithium (1.6 M in hexane, 4.6 mL, 7.4 mmol) was added. The mixture was stirred for 4 h and quenched by the addition of benzophenone (0.64 g, 3.54 mmol). After stirring for 1 h 2N NH_4Cl was added and the mixture was extracted with dichloromethane twice. The combined organic layers were washed with brine and dried over Mg_2SO_4. After removal of the solvent the C_2-diol was recrystallized from water/ethanol affording **2.1a** as colorless crystals (1.1 g, 2.3 mmol, 67 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.61 (s, 4H), 5.17 (br, 2OH), 6.61 (d, *J* = 8.1 Hz, 2H), 7.2 (m, 21H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 48.01 (t), 78.03 (s), 122.76 (d), 126.02 (d), 126.52 (d), 127.86 (d), 136.84 (s), 146.48 (d), 157.34 (s)

2-(6-Methyl-2-pyridinyl)-1,1,3,3-tetraphenyl-1,3-propanediol 2.7a

The monoadduct **2.3a** (0.95 g, 3.29 mmol) was dissolved in 75 mL of dry THF and cooled to 0°C. Subsequently, *n*-butyllithium (1.6 M in hexane, 4.5 mL, 7.2 mmol) was added. The red mixture was stirred for 1 min and a solution of benzophenone (0.60 g, 3.3 mmol) in 5 mL of THF was added. Stirring was continued for another hour and the mixture was quenched with 2N NH_4Cl and extracted twice with dichloromethane. The organic layers were combined and dried over Na_2SO_4. After removal of the solvents by means of rotary evaporation the solid mix of C_2- and C_s-product was washed with hot diethyl ether to leave the C_2-product after filtration. The ether was removed affording the C_s-product which was recrystallized from ethyl acetate/hexane (1:4) yielding a colorless solid (0.30 g, 0.64 mmol, 35%): mp146-147°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H), 4.90 (s, 1H), 6.23 (d, *J* = 6.7 Hz,1H), 6.56 (d, *J* = 6.7 Hz, 1H), 6.7-6.8 (m, 9H), 6.9-7.0 (m, 4H), 7.2-7.3 (m, 8H), 8.48 (br, 2OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 23.88 (q), 56.81 (d), 82.35 (s), 120.10 (d), 125.61 (d), 125.94 (d), 126.09 (d), 126.59 (d),127.08 (d), 127.26 (d), 127.76 (d), 135.22 (d), 144.48 (s), 148.10 (d), 154.99 (s),159.91(s). HRMS calcd 471.220; no proper HRMS could be obtained CI(NH_3) gave a molecular ion at m/e 472. Anal. Calcd for $C_{33}H_{29}NO_2$: C, 84.05; H, 6.20; N, 2.97. Found C, 83.36; H, 6.21; N, 2.98.

1-[6-(2-Hydroxy-2-methylpropyl)-2-pyridinyl]-2-methyl-2-propanol 2.1c and with *n*-butyllithium.

The monoadduct **2.3c** (0.78 g, 4.1 mmol) was dissolved in 50 mL of THF and cooled to 0°C. *n*-Butyllithium (1.6 M in hexane, 5.4 mL, 8.6 mmol) was added and the mixture was stirred for 3h before acetone (0.3 g, 5.1 mmol) was added. After stirring for another hour the mixture was quenched with 2N NH_4Cl and extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by means of column chromatography (silica hexane/ethyl acetate (1:1)) yielding a colorless solid that was recrystallized from hexane (0.6 g, 2.7 mmol, 65%). All spectroscopic data were in full accordance with the literature.[5b]

2,4-Dimethyl-3-(6-methyl-2-pyridinyl)-2,4-pentanediol 2.7c.

The pyridine alcohol **2.3c** (0.5 g, 2.4 mmol) was dissolved in 50 mL of THF and cooled to 0°C. *n*-Butyllithium (1.6 M in hexane, 3.1 mL, 5.0 mmol) was added and the mixture was stirred for 2 min before acetone (0.23 g, 3.97 mmol) was added. The solution was stirred for 1h and quenched with 2N NH_4Cl and extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$. After removal of the solvent the formed C_2-diol was crystallized from hexane and the C_s-diol remained in solution. After evaporation of the mother liquor the C_s-diol was purified by means of column chromatography (silica, hexane/ethyl acetate (2:1)) yielding a viscous oil (0.06 g, 0.23 mmol, 9%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (s, 6H), 1.40 (s, 6H), 2.48 (s, 3H), 2.70 (s, 1H), 5.3 (br, 2OH), 6.85 (d, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 7.45 (dd, *J* = 8.1 Hz, *J* = 7.7 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 24.30 (q), 31.52 (q), 31.60 (q), 61.79 (d), 74.11 (s), 121.12 (d), 123.31 (d), 136.68 (d), 156.84 (s), 161.97 (s).

9-({6-[(9-Hydroxy-9*H*-fluoren-9-yl)methyl]-2-pyridinyl}methyl)-9*H*-fluoren-9-ol 2.1d with *n*-butyllithium.

To a stirred solution of **2.3d** (0.3 g, 1.0 mmol) in 50 mL of THF at 0°C was added *n*-butyllithium (1.6 M in hexane, 1.4 mL, 2.2 mmol). The mixture was stirred for 3h and subsequently 9-fluorenone (0.2 g, 1.1 mmol) in 5 mL of THF was added. The mixture was stirred for 2h and quenched with 2N NH_4Cl. The solution was extracted twice with ethyl acetate and the combined organic layers were washed with brine and dried over $MgSO_4$. After column chromatography (silica hexane/ethyl acetate (2:1)) the solid was recrystallized from ethyl acetate/hexane (1:5) yielding **2.1d** as slightly yellow crystals (0.2 g, 0.4 mmol, 40%). All spectroscopic data were in full accordance with the literature.[5b]

Preparation of KDA[28]

To a stirred solution of potassium t-butoxide (0.90 g, 8.0 mmol) in 50 mL of THF was added diisopropylamide (0.81 g, 8.0 mmol) and the mixture was cooled to –100°C. *n*-Butyllithium (1.6 M in hexane, 5.0 mL, 8.0 mmol) was added over a period of 10 min and the solution was stirred for 30 min before use.

2-({6-[(2-Hydroxy-2-adamantyl)methyl]-2-pyridinyl}methyl)-2-adamantanol 2.1b with KDA.

The monoadduct **2.3b** (0.5 g, 1.9 mmol) was dissolved in 25 mL of THF and cooled to –50°C. A freshly prepared potassium-diisopropylamide solution (0.16 M in THF, 4.0 mmol, 25 mL) was added by canula. Stirring was continued for 15 min before adamantanone (0.3 g, 2.0 mmol) in 5 mL of THF was added. After 1 h the mixture was quenched with 2N NH_4Cl, extracted with dichloromethane twice and dried over $MgSO_4$. After filtration the solvents were removed under reduced pressure to obtain **2.1b** as a solid that was recrystallized from ethanol yielding colorless needles (0.75 g, 1.8 mmol, 95%). All spectroscopic data were in accordance with the data found previously.

2-[6-(2-Hydroxy-2,2-diphenylethyl)-2-pyridinyl]-1,1-diphenyl-1-ethanol 2.1a with KDA

To a stirred solution of the monoadduct **2.3a** (0.52 g, 1.80 mmol) in 50 mL of THF at –70°C was added a freshly prepared solution of KDA (0.25 M in THF, 14.8 mL, 3.7 mmol). The red solution was stirred for 15 min and benzophenone (1.81 g, 0.33 mmol) in 5 mL of THF was added. Stirring was continued for 1h allowing the reaction mixture to reach –10°C, and it was quenched with 2N NH_4Cl. The product was isolated by extraction with dichloromethane twice. The organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvents the product was recrystallized from water/ethanol affording **2.1a** as colorless crystals (0.76 g, 1.62 mmol, 90 %). All experimental data were in accordance with the data reported above.

1-[6-(2-Hydroxy-2-methylpropyl)-2-pyridinyl]-2-methyl-2-propanol 2.1c with KDA.

To a stirred solution of monoadduct **2.3c** (0.47 g, 2.85 mmol) in 25 mL of THF at –60°C was added KDA (0.57M in THF, 12.5 mL, 7.13 mmol). The mixture was stirred at this temperature for 15 min and cooled to –80°C. Acetone (0.33 g, 5.7 mmol) was added and stirring remained for 1 h allowing the mixture to reach ambient temperature. The reaction mixture was quenched with 2N NH_4Cl and extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried with $MgSO_4$. Column chromatography (silica hexane/ethyl acetate (1:1)) afforded **2.1c** as a colorless solid (0.45 g, 2.0 mmol, 71%). All experimental data were in accordance with the data reported above.

9-({6-[(9-Hydroxy-9*H*-fluoren-9-yl)methyl]-2-pyridinyl}methyl)-9*H*-fluoren-9-ol 2.1d with KDA. To a solution of **2.3d** (0.50 g, 1.7 mmol) in 25 mL of THF at –60°C was added KDA (0.57M in THF, 7.6 mL, 4.4 mmol). After stirring for 30 min the mixture was cooled to –80°C and fluorenone (0.31 g, 1.7 mmol) was added. Stirring remained at –80°C for 1 h and subsequently allowed to reach ambient temperature overnight. The reaction mixture was quenched with 2N NH_4Cl and extracted twice with ethyl acetate. The combined organic

layers were washed with brine and dried with $MgSO_4$. Column chromatography (silica hexane/ethyl acetate (2:1)) afforded **2.1d** as slightly yellow crystals (0.58 g, 1.2 mmol, 75%). All experimental data were in accordance with the data reported above.

1,1-Diphenyl-2-(2-pyridinyl)-1-ethanol 2.11a

To a solution of 2-picoline **2.10** (3.9 g, 42 mmol) in 100 mL of THF at –60°C was added *n*-butyllithium (1.6 M in hexane, 26.3 mL, 42.1 mmol) and the mixture was stirred for 30 min. A solution of benzophenone (7.6 g, 42 mmol) in 10 mL of THF was added. Stirring was continued for 1h allowing the mixture to reach ambient temperature. The mixture was quenched with 2N NH_4Cl, extracted twice with ethyl acetate and the combined organic layers were dried over $MgSO_4$. The product was recrystallized from ethanol yielding a colorless solid (10.8 g, 39.4 mmol, 94 %): mp 155-156°C; IR (KBr): 3200, 3000, 1600, 1580, 1450, 1100, 850, 800, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.70 (s, 2H), 7.05 (m, 2H), 7.14 (m, 2H), 7.24 (t, *J* = 8.1 Hz, 4H), 7.47 (m, 5H), 7.74 (br, OH), 8.37 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 46.89 (t), 78.27 (s), 121.37 (d), 124.52 (d), 126.09 (d), 126.32 (d), 127.77 (d),136.76 (d), 147.11 (s), 147.81 (d), 159.17 (s). HRMS calcd 275.131; found 275.132 Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found C, 82.37; H, 6.23; N, 5.05.

2-(2-Pyridinylmethyl)-2-adamantanol 2.11b

2-picoline **2.10** (0.93 g, 10.0 mmol) was dissolved in 75 mL of THF and cooled to –60°C. Subsequently, *n*-butyllithium (1.6 M in hexane, 6.9 mL, 11 mmol) was added and stirring was continued for 30 min. Adamantanone (1.65 g, 11.0 mmol) in 5mL of THF was slowly added and the reaction mixture was stirred for 1 h. After the reaction was quenched with 2N NH_4Cl the solution was extracted twice with ethyl acetate and the combined organic layers were dried over $MgSO_4$. The product was purified by means of column chromatography (silica, hexane/diethyl ether (3:1)) yielding **2.11b** as a colorless solid (1.82 g, 7.4 mmol, 74%): mp 87-88°C; IR (KBr): 3300, 2900, 1600, 1590, 1400, 950, 800 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.4-2.0 (m, 12H), 2.33 (d, *J* =11.0 Hz, 2H), 3.14 (s, 2H), 6.05 (br, OH), 7.15 (m, 2H), 7.61 (t, *J* = 7.7 Hz, 1H), 8.50 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 27.31 (d), 27.36 (d), 32.70 (t), 34.59 (t), 37.18 (d), 38.36 (t), 43.57 (t), 75.37 (s), 121.25 (d), 124.39 (d), 136.59 (d), 148.33 (d), 159.59 (s); HRMS calcd 243.162, found 243.163. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.95; H, 8.79; N, 5.81.

2-Methyl-1-(2-pyridinyl)-2-propanol 2.11c

To a stirred solution of 2-picoline **2.10** (0.7 g, 7.4 mmol) in 50 mL of THF at –50°C was added *n*-butyllithium (1.6 M in hexane, 5.0 mL, 8.1 mmol) followed by the addition of acetone after stirring for 15 min. Stirring was continued for 15 min and the solution was

quenched with NH_4Cl, extracted with ethyl acetate twice. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was obtained after distillation by means of kugelrohr (60°C, 0.05 mm Hg) affording **2.11c** (0.85 g, 5.63 mmol, 76 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (s, 6H), 2.84 (s, 2H), 5.6 (br, OH), 7.05 (d, *J* = 8.1 Hz, 1H), 7.10 (m, 1H), 7.55 (t, *J* = 8.1 Hz, 1H), 8.42 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 29.33 (q), 48.48 (t), 70.55 (s), 121.32 (d), 124.23 (d), 136.61 (d), 148.23 (d), 159.82 (s)

9-({6-[(9-Hydroxy-9*H*-fluoren-9-yl)methyl]-2-pyridinyl}methyl)-9*H*-fluoren-9-ol 2.11d

2-picoline **2.10** (1.38 g, 14.8 mmol) was dissolved in 75 mL of THF and cooled to –60°C. *n*-Butyllithium (1.6 M in hexane, 9.3 mL, 15 mmol) was added and the mixture was stirred for 15 min before a solution of 9-fluorenone (2.7 g, 15 mmol) in 15 mL of THF was added. The mixture was allowed to reach r.t. overnight. After addition of 50 mL 2N NH_4Cl the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. After column chromatography (silica, hexane/ethyl acetate (3:1)) **2.11d** was isolated as a white solid (3.44 g, 12.6 mmol, 85%). mp 87-88°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.22(s, 2H), 6.89 (d, *J* = 7.7 Hz,1H), 6.96 (d, *J* = 7.7 Hz, 2H), 7.11 (t, *J* = 7.7 Hz, 2H), 7.27 (m, 3H), 7.35 (br, OH), 7.59 (m, 3H), 8.61 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 45.71 (t), 81.80 (s), 119.67 (d), 122.05 (d), 123.65 (d), 124.73 (d), 127.34 (d), 128.39 (d), 136.92 (d), 138.90 (s), 147.94 (d), 148.83 (s), 159.20 (s).

1,1,3,3-Tetraphenyl-2-(2-pyridinyl)-1,3-propanediol 2.12a

To a solution of the monoadduct **2.11a** (1.0 g, 3.6 mmol) in 50 mL of THF at r.t. was added *n*-butyllithium (1.6 M in hexane, 4.8 mL, 7.7 mmol). The mixture was stirred for 15 min and benzophenone (0.66 g, 3.63 mmol) in 5 mL of THF was added. The mixture was stirred overnight. The mixture was quenched with 2N NH_4Cl and extracted with dichloromethane the organic layer was dried over $MgSO_4$. The mixture was concentrated and the solid was washed with hot methanol and recrystallized from ethyl acetate/hexane yielding a colorless solid (0.55 g, 1.20 mmol, 33%): mp 143-144°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.02 (s, 1H), 6.53 (d, *J* = 7.7 Hz,1H), 6.8-7.1 (m, 14H), 7.3 (m, 8H), 8.21 (d, *J* = 4.8 Hz, 1H), 8.27 (br, 2OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 57.02 (d), 82.41 (s), 120.69 (d), 125.67 (d), 125.75 (d), 125.96 (d), 126.63 (d),127.13 (d), 127.34 (d), 127.87 (d), 134.86 (d), 144.48 (s), 146.27 (d), 148.07 (s),160.90 (s). HRMS calcd 457.204; no proper HRMS could be obtained. CI(NH_3) gave molecular ions at m/e 183 and 276. Anal. Calcd for $C_{32}H_{27}NO_2$: C, 84.00; H, 5.95; N, 3.06. Found C, 83.87; H, 5.99; N, 3.11.

2-[(2-Hydroxy-2-adamantyl)(2-pyridinyl)methyl]-2-adamantanol 2.12b

A solution of *n*-butyllithium (1.6 M in hexane, 6.3 mL, 10 mmol) was added to a stirred solution of monoadduct **2.11b** (1.2 g, 5.0 mmol) in 75 mL of THF at 0°C. Stirring was

continued for 30 min and adamantanone (0.77 g, 5.13 mmol) in 5 mL of THF was added. The mixture was stirred for another hour and quenched with 2N NH_4Cl. The solution was extracted twice with dichloromethane, the combined organic layers were dried over $MgSO_4$. After concentration of the solution the solid was washed with hot hexane leaving **2.12b** as a white solid (0.51 g, 1.30 mmol, 26%): mp 183-184°C; IR (KBr): 3400, 2950, 1650, 1630, 1450, 1100, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.82 (s, 2H), 1.21 (m, 3H), 1.46 (m, 4H) 1.6-1.9 (m, 13H), 2.05 (d, *J* = 12.1 Hz, 2H), 2.23 (d, *J* = 12.1 Hz, 2H), 2.44 (m, 4H), 3.98 (s, 1H), 6.82 (s, 2OH), 7.19 (m, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.59 (m, 1H), 8.59 (d., *J* = 5.1 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 26.59 (d), 27.03 (d), 32.90 (t), 32.97 (t), 34.28 (t), 35.17 (t), 36.90 (d), 37.72 (d), 38.06 (t), 47.98 (d), 80.33 (s), 121.46 (d), 126.47 (d), 136.05 (d), 148.68 (d), 161.85 (s); HRMS calcd 393.267; no proper HRMS could be obtained. CI(NH3) gave a molecular ion at m/e 394. Anal. Calcd for $C_{26}H_{35}NO_2$: C, 79.35; H, 8.96; N, 3.56. Found C, 78.90; H, 9.09; N, 3.64.

2,4-Dimethyl-3-(2-pyridinyl)-2,4-pentanediol 2.12c

To a stirred solution of **2.11c** (0.36 g, 2.38 mmol) in 50 mL of THF at –30°C was added *n-but*yllithium (1.6 M in hexane, 3.0 mL, 4.9 mmol). The solution was stirred for 30 min and acetone (0.17 g, 2.93 mmol) was added. After stirring for 1 h the mixture was quenched with 2N NH_4Cl. The solution was extracted twice with ethyl acetate and the combined organic layers were dried over $MgSO_4$. The starting material was removed by means of kugelrohr distillation (80°C, 0.05 mm Hg) and the residue was purified by means of column chromatography (silica, hexane/ethyl acetate (1:1)) affording **2.12c** as a colorless oil (0.15 g, 0.72 mmol, 30%): ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (s, 6H), 1.37 (s, 6H), 2.74 (s, 1H) 5.11 (br, 2OH), 7.05 (d, *J* = 7.7 Hz, 1H), 7.13 (m, 1H), 7.58 (dd, *J* = 7.7 Hz, *J* = 7.7 Hz, 1H), 8.45 (d., *J* = 4.0 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 31.35 (q), 31.58 (q), 62.15 (d), 74.22 (s), 121.63 (d), 126.33 (d), 136.45 (d), 147.92 (d), 162.68 (s); HRMS: calcd. 209.141; found 209.141. Anal. calcd. for $C_{12}H_{19}NO_2$: C 68.85, H 9.16, N 6.70; found C 68.65, H 9.09, N 6.41.

(1*R*,2*S*)-1,7,7-Trimethyl-2-[(6-methyl-2-pyridinyl)methyl]bicyclo[2.2.1]heptan-2-ol 2.3e

To a solution of 2,6-lutidine **2.2** (6.0 g, 56 mmol) in 250 mL of THF at –60°C was added *n*-butyllithium (1.6 M in hexane, 38.5 mL, 61.6 mmol). The mixture was stirred at –60°C for 30 min and (*R*)-(+)-camphor (8.5 g, 56 mmol) in 20 mL of THF was added. Stirring was continued for 1 h at –60°C. The mixture was quenched with 1N HCl, stirred for 30 min and neutralized with 2N NaOH. The solution was extracted with ethyl acetate twice and the combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvents in vacuo the product was purified by means of Kugelrohr distillation (75°C, 0.4 mm Hg) yielding **2.3e** as a colorless solid (13.0 g, 50.1 mmol, 90%): mp 38-39°C; $[\alpha]^{23}_D$ –28.7 (*c*

1.5, acetone); IR (KBr): 3300, 3000, 1610, 1600, 1450, 1100, 830, 800 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.45 (s, 3H), 0.76 (s, 3H), 1.05 (m, 1H), 1.07 (s, 3H), 1.30 (m, 1H), 1.41 (m, 2H), 1.63 (m, 2H), 1.98 (m, 1H), 2.44 (s, 3H), 2.88 (s, 2H), 6.65 (br, OH), 6.91 (d, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 7.7 Hz, *J* = 7.7 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 11.14 (q), 20.90 (q), 21.34 (q), 24.15 (q), 27.10 (t), 30.69 (t), 44.88 (t), 47.36 (d), 49.48 (s), 52.23 (s), 81.07 (s), 120.83 (d), 121.11 (d), 136.94 (d), 156.81 (s), 159.67 (s). HRMS calcd 259.194; found 259.194 Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found C, 78.75; H, 9.78; N, 5.54.

(1*R*,2*S*)-2-[(6-{[(1*R*,2*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methyl}-2-pyridinyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 2.1e with *n*-butyllithium

The monoadduct **2.3e** (1.0 g, 3.9 mmol) was dissolved in 50 mL of THF and cooled to –40°C. *n*-Butyllithium (1.6 M in hexane, 2.6 mL, 4.2 mmol) was added and the mixture was stirred for 3 h at –40°C. After cooling to –60°C (*R*)-(+)-camphor (0.59 g, 3.88 mmol) in 5 mL of THF was added and stirring was continued overnight allowing the mixture to reach ambient temperature. The mixture was quenched with 2N NH_4Cl and extracted with dichloromethane twice. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by means of column chromatography (SiO_2, hexane/diethyl ether (9:1)) yielding **2.1e** as a colorless solid, which was recrystallized from ethanol/water (2:1) (0.95 g, 2.31 mmol, 60%): mp 124-125°C; $[\alpha]^{23}_D$ –98.8 (*c* 2.5, acetone); IR (KBr): 3450, 3000, 1630, 1620, 1500, 1060, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.51 (s, 6H), 0.77 (s, 6H), 1.04 (s, 6H), 1.10 (m, 2H), 1.44 (m, 6H), 1.68 (m, 4H), 1.94 (m, 2H), 2.91 (s, 4H), 4.44 (br, 2OH), 7.04 (d, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 10.83 (q), 20.93 (q), 21.37 (q), 27.05 (t), 30.58 (t), 44.93 (t), 45.77 (t), 46.83 (d), 49.35 (s), 52.46 (s), 80.81 (s), 122.50 (d), 137.16 (d), 159.14 (s). HRMS calcd 411.314; found 411.314. Anal. Calcd for $C_{27}H_{41}NO_2$: C, 78.78; H, 10.04; N, 3.40. Found C, 78.64; H, 9.82; N, 3.42.

(1*R*,2*S*)-1,7,7-Trimethyl-2-(2-pyridinylmethyl)bicyclo[2.2.1]heptan-2-ol 2.11e

n-Butyllithium (1.6 M in hexane, 21.8 mL, 35 mmol) was added to a stirred solution of 2-methylpyridine **2.10** (3.24 g, 34.8 mmol) in 75 mL of THF at –60°C. After stirring for 30 min a solution of (*R*)-(+)-camphor (5.4 g, 35 mmol) in 5 mL of THF was added by syringe. Stirring was continued for 3 h allowing the mixture to reach rt. The mixture was quenched with 2N NH_4Cl and extracted twice with ethyl acetate, after which the combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent, the product was purified by Kugelrohr distillation (120°C, 0.1 mmHg) yielding **2.11e** as a colorless oil (6.18 g, 25.2 mmol, 72%): $[\alpha]^{23}_D$ -15.9 (*c* 0.6, acetone); IR (KBr): 3300, 2950, 1650, 1630, 1450, 1050, 800, 500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.48 (s, 3H), 0.81 (s,

3H), 0.98 (d, *J* = 13.2 Hz, 1H), 1.09 (m, 1H), 1.11 (s, 3H), 1.41 (m, 3H), 1.70 (m, 2H), 2.06 (d, *J* = 13.2 Hz, 1H), 2.91 (s, 2H), 6.31 (br, OH), 7.17 (m, 2H), 7.61 (t, *J* = 7.7 Hz, 1H), 8.45 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 11.04 (q), 20.88 (q), 21.27 (q), 27.07 (t), 30.64 (t), 44.85 (d), 45.08 (t), 47.29 (t), 49.43 (s), 52.81 (s), 81.07 (s), 121.30 (d), 124.23 (d), 136.66 (d), 147.84 (d), 160.40 (s). HRMS calcd 245.178; found 245.178 Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found C, 78.33; H, 9.54; N, 5.44.

Reaction of 2.11e with *n*-butyllithium and benzophenone to obtain 2.11a

To a stirred solution of **2.11e** (0.65 g, 2.65 mmol) in 50 mL of THF at –60°C was added *n*-butyllithium (1.6 M in hexane, 3.5 mL, 5.6 mmol) followed after 5 min by the addition of benzophenone (0.49 g, 2.69 mmol). The mixture was stirred for 1h allowing to reach ambient temperature and quenched with 2N NH_4Cl. The solution was extracted with dichloromethane twice and the organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent the product **2.11a** and the starting material **2.11e** were separated by means of crystallization from hexane from which the benzophenone adduct **2.11a** crystallizes as colorless needles (0.29 g, 1.05 mmol, 40%): All experimental data were in accordance with the data reported above.

(1*R*,2*S*)-2-[(6-{[(1*R*,2*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methyl}-2-pyridinyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 2.1e with KDA

Monoadduct **2.3e** (0.5 g, 1.9 mmol) was dissolved in 50 mL of THF and a solution of KDA (0.16 M in THF, 25 mL, 4.0 mmol) was added at –50°C. After stirring for 15 min a solution of (*R*)-(+)-camphor (0.3 g, 2.0 mmol) in 5 mL of THF was added. Stirring was continued for 2h while the solution was allowed to reach ambient temperature. The mixture was quenched with 2N NH_4Cl and extracted twice with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was recrystallized from ethanol/water (2:1) (0.75 g, 1.82 mmol, 95%).

Crystal Structure of 2.1e

Crystal Data: Formula: $C_{27}H_{41}NO_2$, M = 411.63, The crystal, used for characterization and data collection, was a parallelepiped of approximate size 0.10 x 0.40 x 0.52 mm. Monoclinic, $P2_1$, *a* = 7.116(1), *b* = 27.467(2), *c* = 12.467(1) Å, β= 97.167(7)°, *V* = 2417.7(4) Å, *Z* = 4, D_x = 1.131 g cm^{-1}, λ(MoK$\bar{\alpha}$) = 0.71073 Å, μ = 0.70 cm , *F*(000) = 904. *Data collection*: The data were collected on an Enraf-Nonius *CAD*-4*F* diffractometer (Mo tube, 50 kV, 40 mA, monochromated Mo-Kα radiation, Δω = 1.00 + 0.34 tg θ); T = 130 K, range 17.92° < θ < 20.15°, reflections collected*:* 5113 independent reflections 4693. *Solutions and refinement*: The structure was solved by Patterson methods and extension of the model was accomplished by direct methods applied to difference structure factors using the program *DIRDIF*. Refined

anisotropically by full-matrix least squares based on F^2 (SHELXL); data/parameters 4693/869 ; $R(F)$ = 0.0421 [$F_o \geq 4.0\ \sigma(F_o)$], $wR(F^2)$ = 0.1107 [$F^2>0$]; absolute-structure parameters; maximal residual electron density (±0.24(5) e/Å^3). The program PLATON has been used for graphical representations of the crystal structure.

Table 2.3 : *Interatomic distances and selected bond angles for compound **2.1e.***

Interatomic Distances (Å)					
O(1)[a]	-C(7)	1.441(4)[b]	C(6)	-C(7)	1.557(4)
O(2)	-C(18)	1.438(4)	C(17)	-C(18)	1.541(4)
N(1)	-C(1)	1.336(4)	H(61)	-O(1)	0.839
N(1)	-C(5)	1.361(4)	H(62)	-O(2)	0.791
C(1)	-C(17)	1.513(4)	H(61)	-N(1)	2.022
C(5)	-C(6)	1.495(4)	H(62)	-N(1)	2.110

Bond Angles (deg.)							
C(1)[a]	-N(1)	-C(5)	120.0(2)	C(1)	-C(17)	-C(18)	115.6(2)
N(1)	-C(1)	-C(17)	115.4(2)	O(2)	-C(18)	-C(17)	107.6(2)
C(2)	-C(1)	-C(17)	122.7(3)	O(2)	-C(18)	-C(19)	107.8(2)
N(1)	-C(5)	-C(6)	115.9(2)	O(2)	-C(18)	-C(23)	111.8(2)
C(4)	-C(5)	-C(6)	123.8(3)	C(17)	-C(18)	-C(19)	110.6(2)
C(5)	-C(6)	-C(7)	116.1(2)	C(17)	-C(18)	-C(23)	116.5(2)
O(1)	-C(7)	-C(6)	106.9(2)	H(61)	-O(1)	–C(7)	107.12
O(1)	-C(7)	-C(8)	107.9(2)	H(62)	-O(2)	–C(18)	108.92
O(1)	-C(7)	-C(12)	111.2(2)	O(1)	-H(61)	-N(1)	145.52
C(6)	-C(7)	-C(8)	110.6(2)	O(2)	-H(62)	-N(1)	148.13
C(6)	-C(7)	-C(12)	116.5(2)				

[a] The numbering for the crystal data does not follow the numbering used in nomenclature.

[b] Standard deviation in parentheses.

(1*R*,2*RS*)-1,3,3-Trimethyl-2-[(6-methyl-2-pyridinyl)methyl]bicyclo[2.2.1]-heptan-2-ol 2.3f

2,6-Lutidine **2.2** (1.0 g, 0.9 mmol) in 50 mL of THF was lithiated with *n-bu*tyllithium (1.6 M in hexane, 6.2 mL, 10 mmol) at –60°C. After stirring for 10 min (*R*)-(-)-fenchone (1.4 g, 9.2 mmol) in 5 ml of THF was added and stirring was continued for 1h. Workup was done with NH_4Cl and ethyl acetate yielding **2.3f** as a mixture of the *exo* and *endo* isomers (1.9 g, 7.3 mmol, 79%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.67 (s, 3H), 0.76 (s, 3H), 0.86 (s, 3H), 0.90(s, 3H), 0.99 (s, 3H), 1.05 (s, 3H), 1.1-1.8 (m, 12H), 2.1-2.3 (m, 2H), 2.47 (s, 6H), 2.85 (d, *J* = 15.6, 2H), 2.95 (s, 2H), 3.03 (d, *J* = 15.6, 2H), 6.95 (m, 4H), 7.5 (m, 4H).

(1*R*, 2*R*)-1,3,3-Trimethyl-2-(2-pyridinylmethyl)bicyclo[2.2.1]heptan-2-ol 2.11f

To a stirred solution of 2-picoline **2.10** (1.0 g, 11 mmol) in 50 mL of THF at –50 °C, was added *n*-butyllithium (6.9 mL, 11 mmol) after stirring for 15 min. (*R*)-(-)-fenchone (1.7 g, 11

mmol) in 5 ml of THF was added and stirring continued for 1h. The mixture was quenched with NH_4Cl and extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were evaporated yielding a mixture of the *endo* and *exo* isomers en a ratio of 3:2. The *exo* isomer was selectively crystallized from hexane at –20 °C (1.3 g, 5.4 mmol, 50%): mp 113-114°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.62 (s, 3H), 0.85 (s, 3H), 0.92 (m, 1H), 1.01 (s, 3H), 1.09 (d, *J* = 10.3 Hz, 1H), 1.34 (m, 1H), 1.52 (m, 1H), 1.64 (m, 1H), 1.71 (m, 1H), 2.18 (m, 1H), 2.94 (dd, *J* = 34.4 Hz, *J* = 15.7 Hz, 2H), 7.06 (m, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 8.33 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 17.86 (q), 23.13 (q), 25.37 (t), 28.15 (q), 29.38 (t), 40.77 (t), 41.84 (t), 44.66 (s), 50.11 (t), 52.62 (s), 82.07 (s), 120.83 (d), 124.15 (d), 136.63 (d), 147.03 (d), 162.83 (s). HRMS calcd 245.178; found 245.178. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32 H, 9.45; N, 5.71. Found C, 78.29; H, 9.44; N, 62.

Dichloro[(6-methyl-2-pyridinyl)methyl]cerium 2.17

To a stirred solution of 2,6-lutidine **2.2** (0.1M solution in THF, 10 mL, 1.0 mmol) at –70°C was added *n*-butyllithium (0.63 mL, 1.0 mmol). After stirring for 15 min this solution was added to $CeCl_3$·THF[19] (0.1M solution in THF, 10 mL, 1.0 mmol) at –70°C. The solution was stirred for 1 h at –50°C and used as such for the addition reactions to ketones.

General Procedure for addition of 2.17 to ketones

To a stirred solution of **2.17** (0.05M solution in THF, 20 mL, 1.0 mmol) at –70°C was added a solution of the ketone (1.0 mmol) in 2 mL of THF. Stirring was continued for 3 h after which the solution was quenched with NH_4Cl and extracted with ethyl acetate twice. The combined organic layers were washed with brine and dried over $MgSO_4$.

(1*R*,2*RS*)-1,3,3-Trimethyl-2-[(6-methyl-2-pyridinyl)methyl]bicyclo[2.2.1]-heptan-2-ol 2.3f with $CeCl_3$·THF

According to the above general procedure starting from **2.17** (0.05 M solution in THF, 22 mL, 1.1 mmol) and (*R*)-(-)-fenchone (0.17 g, 1.12 mmol) giving a mixture of *endo* and *exo* isomers **2.3f** in a ratio of 4:1 (0.15 g, 0.58 mmol, 54 %).

(1*RS*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-[(6-methyl-2-pyridinyl)methyl]-cyclohexanol 2.3g

To a solution of 2,6-lutidine **2.2** (0.7 g, 6.5 mmol) in 50 mL of THF at –60°C was added *n*-butyllithium (1.6 M in hexane, 4.1 mL, 6.5 mmol). After stirring for 10 min (-)-menthone (1.0 g, 6.5 mmol) in 5 mL of THF was added. Stirring was continued for 1 h at –60°C before the mixture was quenched with NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. The *cis* and *trans* products in the mixture with a ratio of 2:1 were separated by means of column chromatography (silica, hexane/diethyl ether 10:1) yielding the pure isomers.

***trans*-2.3g** (0.5 g, 2.0 mmol, 30%): mp 60-62°C; $[\alpha]^{23}_{D}$ + 67 °(*c* 0.8, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.72 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 1H), 0.91 (m, 2H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.25 (m, 2H), 1.33 (m, 1H), 1.37 (m, 1H), 1.67 (m, 1H), 1.73 (m, 1H), 2.44 (dq, *J* = 7.0 Hz, *J* = 7.0 Hz, 1H), 2.52 (s, 3H), 2.94 (dd, *J* = 14.0 Hz, *J* = 14.0 Hz, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 7.51 (dd, *J* = 7.0 Hz, *J* = 7.8 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 19.20 (q), 22.26 (q), 23.39 (t), 24.76 (q), 24.78 (q), 30.30 (d), 35.04 (t), 38.86 (t), 47.81 (t), 51.89 (d), 75.55 (s), 120.77 (d), 121.19 (d), 136.94 (d), 157.34 (s), 159.35 (s). HRMS calcd 261.209; found 261.209. Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11 H, 10.41; N, 5.36. Found C, 78.12; H, 10.57; N, 5.12.

***cis*-2.3g** (1.0 g, 3.8 mmol, 59%): mp 64-66°C; $[\alpha]^{23}_{D}$ – 121° (*c* 0.6, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.67 (d, *J* = 6.2 Hz, 3H), 0.75 (m, 2H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.05 (m, 1H), 1.15 (m, 1H), 1.52 (m, 2H), 1.67 (m, 2H), 2.19 (dq, *J* = 6.9 Hz, *J* = 6.9 Hz, 1H), 2.44 (d, *J* = 3.9, 1H), 2.45 (s, 3H), 3.31 (d, *J* = 13.9 Hz, 1H), 6.84 (d, *J* = 7.3 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 6.9 Hz, *J* = 7.7 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 18.04 (q), 20.84 (t), 22.37 (q), 23.78 (q), 24.23 (q), 26.19 (d), 27.65 (d), 35.35 (t), 46.10 (t), 47.44 (t), 51.13 (d), 74.74 (s), 120.57 (d), 121.46 (d), 136.76 (d), 157.10 (s), 159.92 (s). HRMS calcd 261.209; found 261.209 Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11 H, 10.41; N, 5.36. Found C, 78.04; H, 10.39; N, 5.49.

(1*R*,2*S*,5*R*)-1-[(6-{[(1*R*,2*S*,5*R*)-1-Hydroxy-2-isopropyl-5-methylcyclohexyl]methyl}-2-pyridinyl)methyl]-2-isopropyl-5-methylcyclohexanol *cis*-*cis*-2.1g

The monoadduct ***cis*-2.3g** (0.65 g, 2.49 mmol) was dissolved in 50 mL of THF and cooled to 0°C, *n*-butyllithium (1.6 M in hexane, 3.4 mL, 5.4 mmol) was added and the mixture was stirred for 5 min. (-)-Menthone (0.39 g, 2.53 mmol) in 3 mL of THF was added and the mixture was stirred overnight. The mixture was quenched with NH_4Cl and extracted twice with dichloromethane. The combined organic layers were dried over Na_2SO_4. After concentration in vacuo the solid was crystallized from water/ethanol affording ***cis*-*cis*-2.1g** as a colorless solid (0.4 g, 1.0 mmol, 40%): mp 125-126°C; $[\alpha]^{23}_{D}$ – 109 °(*c* 1.3, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.67 (d, *J* = 6.4 Hz, 6H), 0.8 (m, 4H), 0.89 (d, *J* = 6.9 Hz, 6H), 0.94 (d, *J* = 6.6 Hz, 6H), 1.05 (m, 2H), 1.4-1.8 (m, 10H), 2.20 (m, 2H), 2.49 (d, *J* = 13.2 Hz, 2H), 3.32 (d, *J* = 13.2 Hz, 2H), 3.75 (br, 2OH), 6.99 (d, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 18.07 (q), 20.80 (t), 22.26 (q), 23.73 (q), 26.05 (d), 27.63 (d), 35.11 (t), 47.10 (t), 47.36 (t), 51.02 (d), 74.74 (s), 122.30 (d), 136.81 (d), 159.17 (s). HRMS calcd 415.345; found 415.345. Anal. Calcd for $C_{27}H_{45}NO_2$: C, 78.02; H, 10.91; N, 3.37. Found C, 77.91; H, 10.99; N, 3.37.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-[(6-methyl-2-pyridinyl)methyl]cyclohexanol *cis*-2.3g with $CeCl_3$·THF

According to the above general procedure starting from **2.17** (0.05 M solution in THF, 36 mL, 1.8 mmol) and (-)-menthone (0.3 g, 1.8 mmol) affording ***cis*-2.3g** as a colorless solid after column chromatography (silica, hexane/diethyl ether 9:1) (0.21g, 0.8 mmol, 45%). All experimental data were in accordance with the data reported above.

2-{(2-Hydroxy-2-adamantyl)[6-(2-hydroxy-2,2-diphenylethyl)-2-pyridinyl]methyl}-2-adamantanol 2.19

To a stirred solution of the diol **2.7b** (0.5 g, 1.2 mmol) in 50 mL of THF at 0°C was added *n*-butyllithium (1.6 M solution in hexane, 2.7 mL, 4.3 mmol). The solution was stirred for 1 h and subsequently benzophenone (0.2 g, 1.2 mmol) in 5 mL of THF was added. The mixture was allowed to reach ambient temperature overnight. The product was quenched with NH_4Cl and the layers were separated. The water layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was purified by means of column chromatography (silica, hexane/ethyl acetate (25:1)) recovering 57% starting material and yielding **2.19** which was recrystallized from dichloromethane/hexane by slow evaporation of the solvent (0.25 g, 0.42 mmol, 35%); mp 186-188°C; IR (KBr): 3410, 3090, 2910, 1595, 1570, 1450, 1060, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.65 (s, 2H), 1.16 (d, *J* = 10.6 Hz, 2H), 1.31 (d, *J* = 12.8 Hz, 2H), 1.49 (d, *J* = 11.0 Hz, 2H), 1.57-182 (m, 12H), 2.01 (d, *J* = 11.7 Hz, 2H), 2.19 (d, *J* = 11.0 Hz, 2H), 2.38-2.41 (m, 4H), 3.75 (s, 2H), 3.88 (s, 1H), 5.41 (br, 2OH), 6.10 (br, OH), 6.90 (d, *J* = 8.06 Hz, 1H), 7.02 (d, *J* = 7.69 Hz, 1H), 7.11-7.16 (m, 2H), 7.21-7.26 (m, 4H), 7.45 (dd, *J* = 8.06 Hz, *J* = 7.69 Hz, 1H), 7.47-7.50 (m, 4H); ^{13}C NMR (300 MHz, CDCl3): δ 26.49 (d), 26.89 (d), 32.79 (t), 32.93 (t), 34.03 (t), 35.07 (t), 36.98 (d), 37.37 (d), 37.97 (t), 47.52 (d), 47.73 (t), 77.93 (s), 80.25 (s), 122.48 (d), 123.56 (d), 126.07 (d), 126.39 (d), 127.83 (d), 136.40 (d), 146.77 (s), 158.00 (s), 160.32 (s); Anal. calcd. for $C_{40}H_{47}NO_3$: C 81.46, H 8.03, N 2.37; found C 79.89, H 7.83, N 2.33. HRMS calcd. 589.82 no proper HRMS could be obtained but CI(NH_3) gave molecular ions at m/e 438, 420 and 402.

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23 Further assignment of the signals was not necessary for the elucidation of the isomer. However, from *COSY* and *NOESY* spectra the following assignment was obtained: δ 0.72 (Me_a), 0.87 (Me_b), 0.90 (H_d), 0.95 (H_b), 1.03 (Me_c), 1.25 ($H_{d'}$+$H_{e'}$), 1.33 (H_a), 1.37 (H_c), 1.67 (H_e), 1.73 ($H_{b'}$), 2.44 (H_f), 2.52 (CH_3), 2.94 (CH_2).

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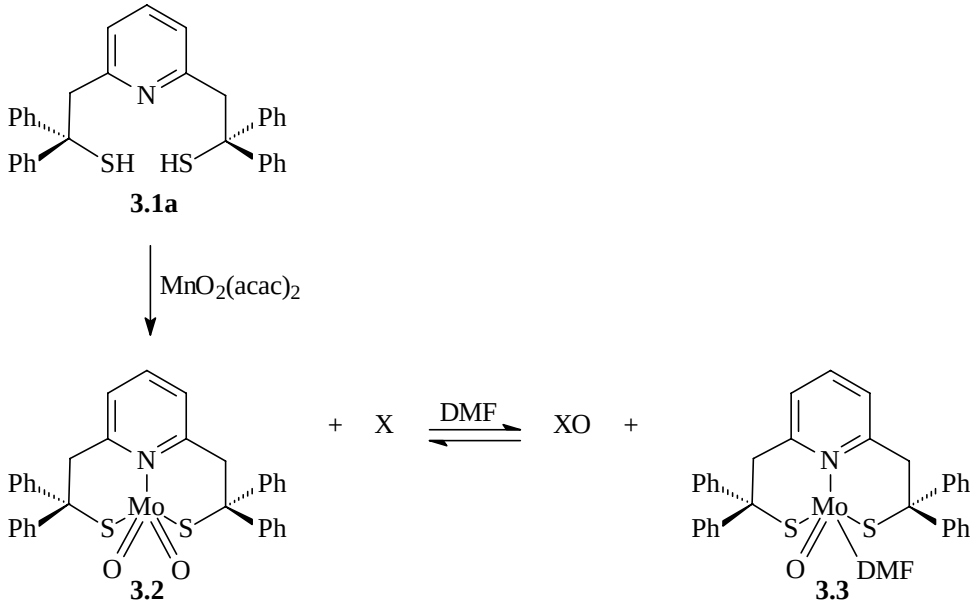
CHAPTER 3

Pyridine Thiols.*

Abstract: A new approach to pyridine thiols has been investigated. It was found that base-induced addition of 2,6-lutidine to thioadamantanone afforded pyridine thiol **3.11b** in a single step. Addition appeared to be carbon-selective and no thiophilic alkylation was observed. The pyridine thiol **3.11b** was converted to the pyridine dithiol **3.1b** in one step. Using the same approach addition to (*R*) and (*S*)-thiofenchone afforded chiral non-racemic pyridine thiols **3.11f** and **3.1f**. Again addition was carbon-selective. Furthermore addition to the thioketone was found to be *exo*-facial selective as was concluded from NMR spectral data (^{1}H, *COSY*, *NOESY*, and *HETCOR*) of the HCl-complex of **3.11f**. The structure of the product determined by means of crystallography was clearly the result *exo*-attack. Unfortunately addition to thiocamphor failed due to enolization of the thioketone. Using Grignard reagent **3.20,** however, enolization occurred only to a moderate extent and pyridine thiol **3.22e** could be isolated in 52% yield.

3.1 Introduction.

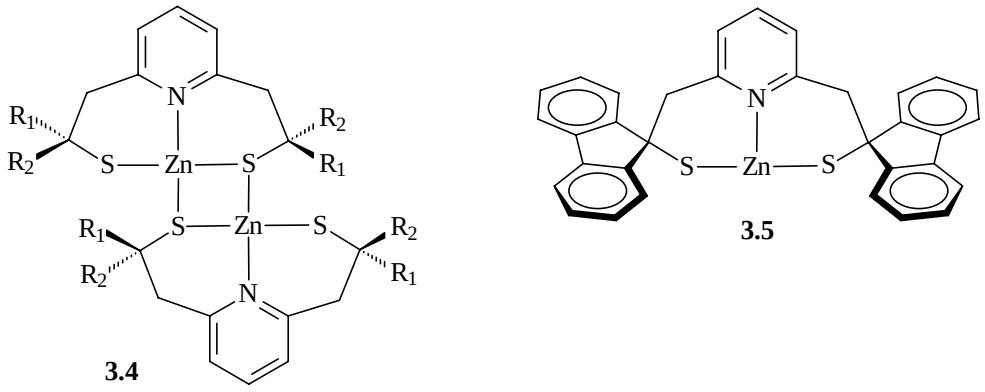
Models for active sites of metalloenzymes can be prepared by using coordination compounds in which the metal is embedded in the cavity of the compound, so mimicking the pocket of the enzyme.[1] Pyridine diols (see Chapter 2) were found to complex metals in this manner and were used as such.[2] Pyridine dithiols (the sulfur analogues of pyridine diols form structurally related complexes. Pyridine dithiol **3.1a,** for example, which was first reported by Berg and Holm,[3] was extensively studied as a model for the molybdenum enzymes. Complexation of the NS_2 ligand **3.1a** with $MoO_2(acac)_2$ in methanol afforded the Mo(VI) complex **3.2** which is, for example, capable of oxidizing triphenylphosphine into its oxide and thiols to their disulfides.[4] The, Mo(IV) species **3.3** formed in this reaction in turn is capable of reducing DMSO to the sulfide and reducing pyridinium-*N*-oxides to the corresponding pyridines (Scheme 3.1).



Scheme 3.1 *Pyridine dithiolate molybdenum complex as active modelsystem for molybdenum enzymes.*

These tridentate pyridine dithiols **3.1** have also been of interest in our group. Complexes derived from these ligands have been studied as models for the catalytic active zinc at the active site of Horse Liver Alcohol Dehydrogenase.[5] Bonding of Zn^{2+} with pyridine dithiols **3.1a** (R_1=R_2=Ph) and **3.1c** (R_1=R_2=Me) proceeds very well. In these cases dimeric rather than monomeric complexes are formed. This problem can be circumvented using pyridine thiol **3.1d** (R_1,R_2=fluorenone), which because of the steric interactions cannot form dimeric intermediates. Unfortunately the Zn^{2+} is so protected that apparently nothing can reach it; no catalytic activity of this complex was observed.[5a] Pyridine dithiols **3.1** are interesting candidates for studies of metal complexes of relevance to the functioning of the

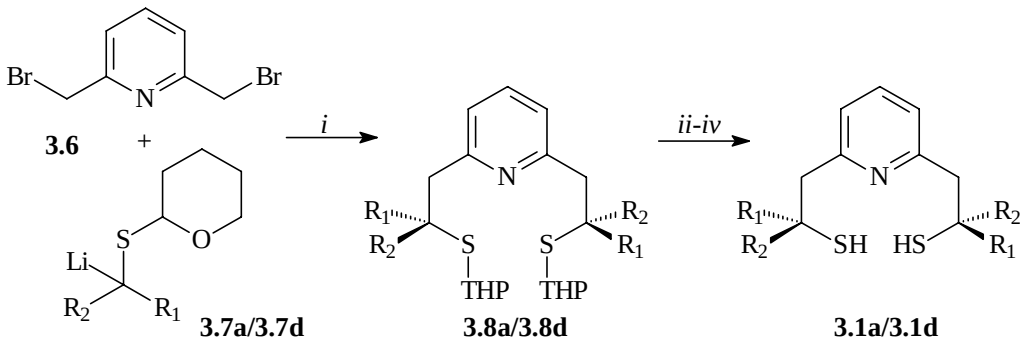
zinc ion in horse liver alcohol dehydrogenase. Tuning of the steric hindrance in the pyridine dithiols by variation of the side groups could afford stable complexes with zinc if these substituents are bulky enough to prevent dimerization. The synthetic approach that was used by Berg[3] and Kaptein[5a] does not allow placement of substituents other than phenyl groups as pointed out below.



Structures 3.4 and **3.5** *Zinc complexes with pyridine dithiols **3.1**.*

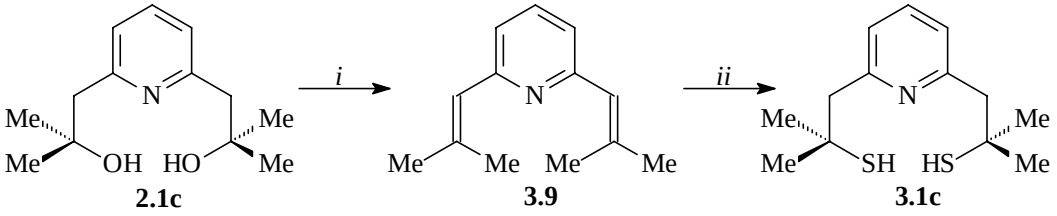
3.2 Approaches for the Synthesis of Pyridine Dithiols.

Pyridine dithiols of this type were synthesized either from a multistep reaction[3] depicted in Scheme 3.2 or from the corresponding pyridine diol (Scheme 3.3).[5]



Scheme 3.2 *Reagents and conditions: i,* Et_2O; *ii* $AgNO_3$/pyr, MeOH/EtOAc; *iii* H_2S; *iv* pH 7 Buffer.

In the first approach the starting material 2,6-bis(hydroxymethylene)pyridine is converted to the dibromide **3.6** and allowed to react with the α-position of a THP (tetrahydropyran) protected thiol **3.7** using *n*-BuLi affording the THP protected dithiol **3.8**. Subsequently the thiol groups are deprotonated affording the pyridine dithiol **3.1**. Drawbacks in this approach are the need for a relative acidic α-proton (so R_1,R_2 must be aromatic; phenyl (**a**), fluorenyl (**b**)) and the presence of a protection and deprotection step.



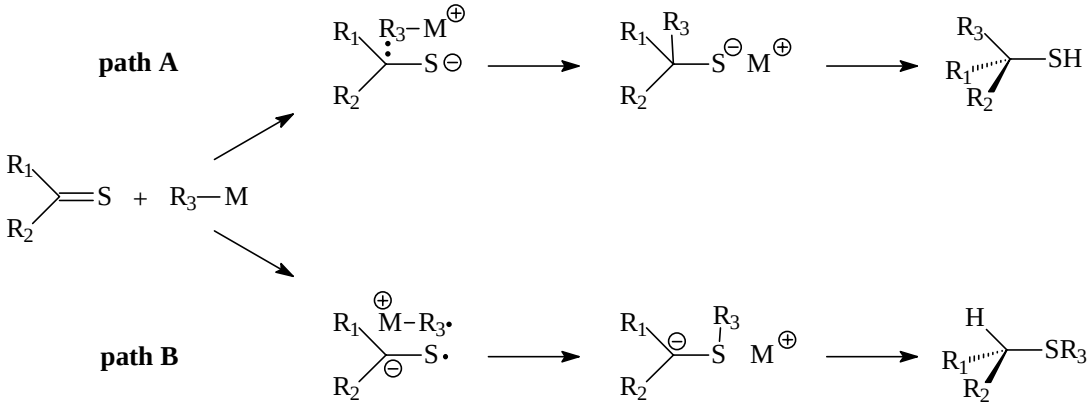
2.1c **3.9** **3.1c**

Scheme 3.3 *Reagents and conditions: i,* H_3PO_4/heat; *ii* $HSCOCH_3$/p-toluenesulfonic acid/MeOH.

The second approach so far has only been successful for tetramethyl ligand **3.1c**. In this approach the diol **2.1c** is dehydrated forming the dialkene **3.9** which upon reaction with thioacetic acid under acidic conditions gives the pyridine dithiol **3.1c** in 48% yield. Starting from 2,6-lutidine an overall yield of 16% is obtained.

3.3 Towards a New Synthetic Approach.

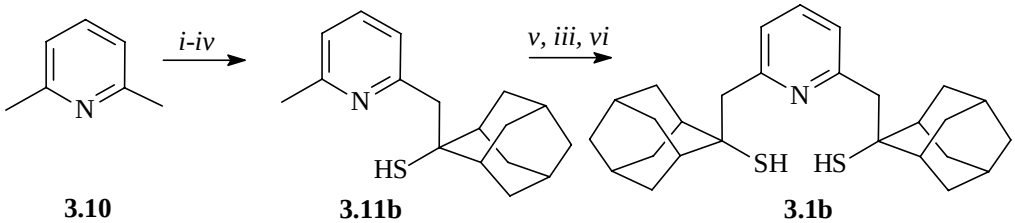
Since both approaches have major drawbacks including low yield, low atom economy, harsh conditions and restrictions with regard to the R_1 and R_2, a new synthetic approach involving direct addition of organometallic compounds to thioketones was investigated. The addition reaction of organometallic compounds to thioketones has been a subject of interest since Beak and Worley "discovered" thiophilic addition.[6] They found that thiobenzophenone reacts with organometallic compounds such as phenyllithium and *n*-butyllithium to give addition products in which the nucleophile is attached to the sulfur. This thiophilic attack seems to be a general reaction pathway for aromatic thioketones (Scheme 3.4; path B).



Scheme 3.4 *Thiophilic addition vs. C-alkylation of thioketones.*

Addition at the carbon atom of the thiocarbonyl group has also been reported (path A). Exclusive C-alkylation, as judged from the literature, seems only possible for aliphatic

thioketones.[6] Furthermore reduction of the thioketone is reported to be a severe side reaction in this process. The competitive C- vs. S-alkylation is highly influenced by the nature of the organometallic species and the reaction conditions used. Alkyllithium reagents usually give a mixture of C and S alkylated products.[7] Grignard reagents in combinations with aliphatic thioketones give C-alkylation.[8] Although C-alkylation of thioketones is not preferred with alkyllithium reagents, the use of them in the synthesis of pyridine thiols would afford a very direct synthetic approach. To minimize the possibility of thiophilic attack aliphatic thioketones will have to be used. For this purpose we synthesized thioadamantanone[9] and used it in the alkylation-reaction with the monolithiated 2,6-lutidine **3.10** (Scheme 3.5).



3.10 **3.11b** **3.1b**

Scheme 3.5 *Reagents and conditions* : *i*, *n*-BuLi (1.1 equiv.), THF, –80 °C; *ii* – 80 °C→ –40 °C; *iii* thioadamantanone; *iv* H_3O^+; *v* *n*-BuLi (2.1 equiv.), THF, – 80 °C; *vi* –80 °C→ –50 °C.

A C-selective alkylation was observed. The thiophilic alkylation product was not obtained at these temperatures. The pyridine thiol **3.11b** could be isolated after hydrolysis of the lithium sulfide salt with 5N HCl. Column chromatography of the crude product afforded the thiol **3.11b** in 76% yield. Further derivatization of the pyridine thiol **3.11b** to the corresponding pyridine dithiol **3.1b** was accomplished by double lithiation of the thiol **3.11b** followed by reaction with thioadamantanone. The hydrolysis of the bis-lithium salt, was more troublesome, due to the stability of the salt as revealed by means of ^{1}H and ^{3}Li NMR. Attempts to hydrolyze the bis-lithium salt with NH_4Cl led to the isolation of the bis-lithium salt. Upon hydrolysis with 5N HCl the dithiol was isolated. Purification of the product by means of column chromatography afforded the pyridine dithiol **3.1b** in 80% yield. Using this new approach the pyridine dithiol **3.1b** can be synthesized in only two steps with an overall yield of 61%. Reaction conditions used in this approach are mild and there is no need for protection and deprotection. An additional advantage is that the 'single-armed' pyridine thiol **3.11b** can be obtained and studied separately.

Suitable crystals for crystallographic determination were grown from a dichloromethane/hexane mixture (Figure 3.1). In the solid state the thiol groups of the pyridine dithiol are situated in a conformation anti to each other, resulting in a slightly distorted C_2-symmetry. Furthermore the thiol groups are turned outside the cavity of the

molecule. It is proposed that upon complexation these thiol groups and the pyridine nitrogen form a cavity in which metals can be complexed.

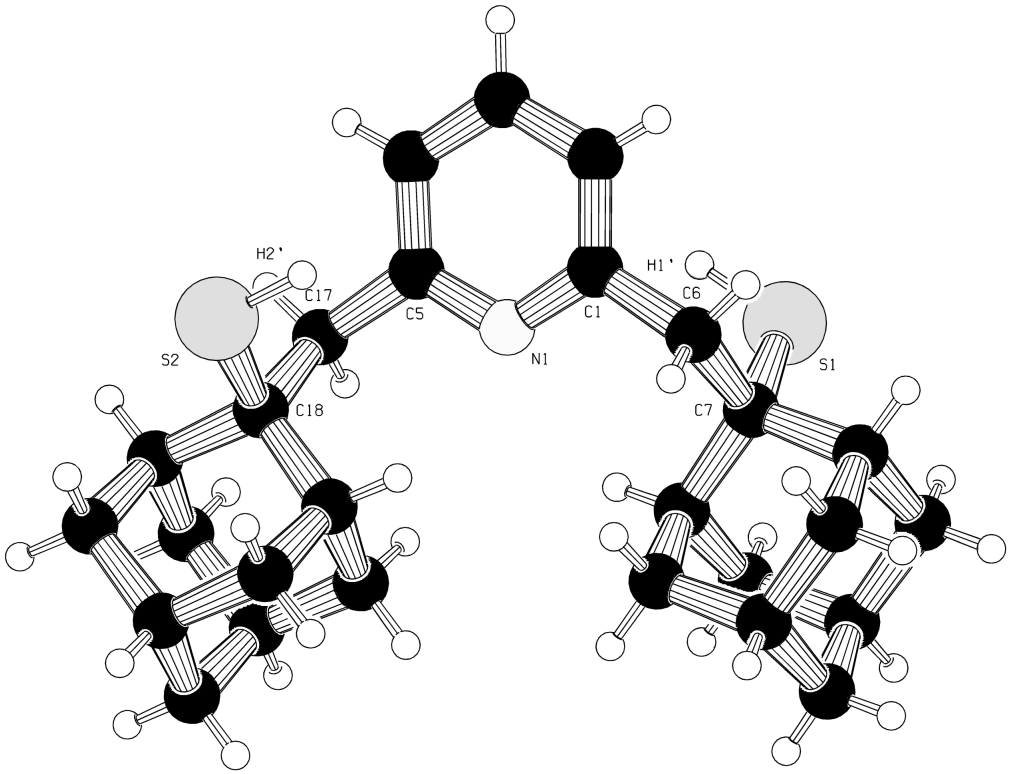
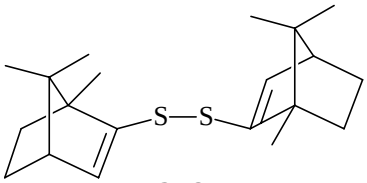


Figure 3.1 *X-ray structure of **3.1b.***

3.4 Chiral Pyridine Thiols.

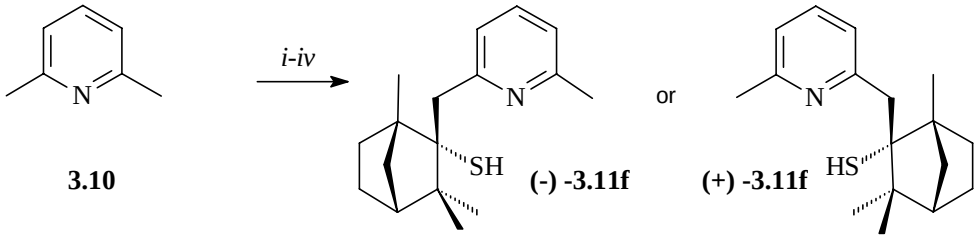
Chiral analogues of the pyridine dithiols **3.1** at the inception of this work were unknown and our next goal was to broaden the new approach to the preparation of chiral non-racemic pyridine thiols starting from chiral thioketones. A few chiral ketones are known and the commercially available *(R)*-thiocamphor seemed to be a good candidate since regioselective C-alkylation of thiocamphor was known.[8] However when thiocamphor was added to the monolithiated lutidine no pyridine thiol could be isolated, just starting materials and some disulfide **3.12**.



3.12

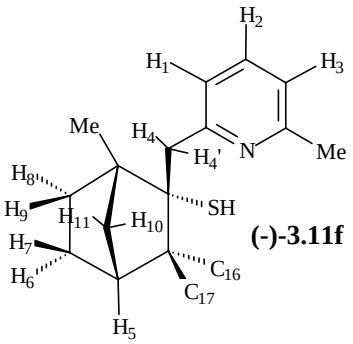
It is clear that thiocamphor fails to undergo addition owing to formation of the thioenolate. Competitive enolate formation in the case that relatively acidic α-protons are present, appears to be a limitation of the direct approach. Therefore (*S*)-thiofenchone, prepared from (*S*)-(+)-fenchone (ee = 98%) or (*R*)-thiofenchone (from (*R*)-(–)-fenchone (ee =

96%))[10] were synthesized and used for the preparation of the single-armed pyridine thiol **3.11f**. Using the previously described approach the mono condensation product could be isolated in 89% yield as either enantiomer (-)-**3.11f** or (+)-**3.11f** depending on the thioketone used (Scheme 3.6). Surprisingly a single isomer was formed, whereas with fenchone itself a mixture of equal amounts of *exo* and *endo* isomers is formed (Chapter 2)



Scheme 3.6 *Reagents and conditions : i, n*-BuLi (1.1 equiv.), THF, –60 °C; *ii* – 60 °C→ –40 °C; *iii* (*R*) or (*S)*-thiofenchone; *iv* H_3O^+.

By means of *HETCOR*, *COSY* and *NOESY* experiments on (–)-**3.11f** addition was established to have taken place from the *exo* side of thiofenchone. This could be determined more clearly from spectra of the (–)-**3.11f**·HCl complex of the monothiol adduct, prepared by passing HCl gas through a solution of (–)-**3.11f** in dichloromethane.



Structure (–)-***3.11f***

This complex has a locked conformation on the NMR chemical shift scale and an AB system is observed for the benzylic protons H_4 and H_4' (see structure (–)-**3.11f** for the numbering scheme, chosen for simplicity of illustration), whereas for the free ligand a singlet was found. The pyridine protons H_1, H_2, and H_3 of the HCl-complex are shifted 0.50, 0.67, and 1.74 ppm downfield respectively. This is consistent with protonation of the pyridine nitrogen. Furthermore, most protons of the thiofenchone moiety are shifted downfield relative to the uncomplexed ligand, and assignment of the specific protons is simplified.

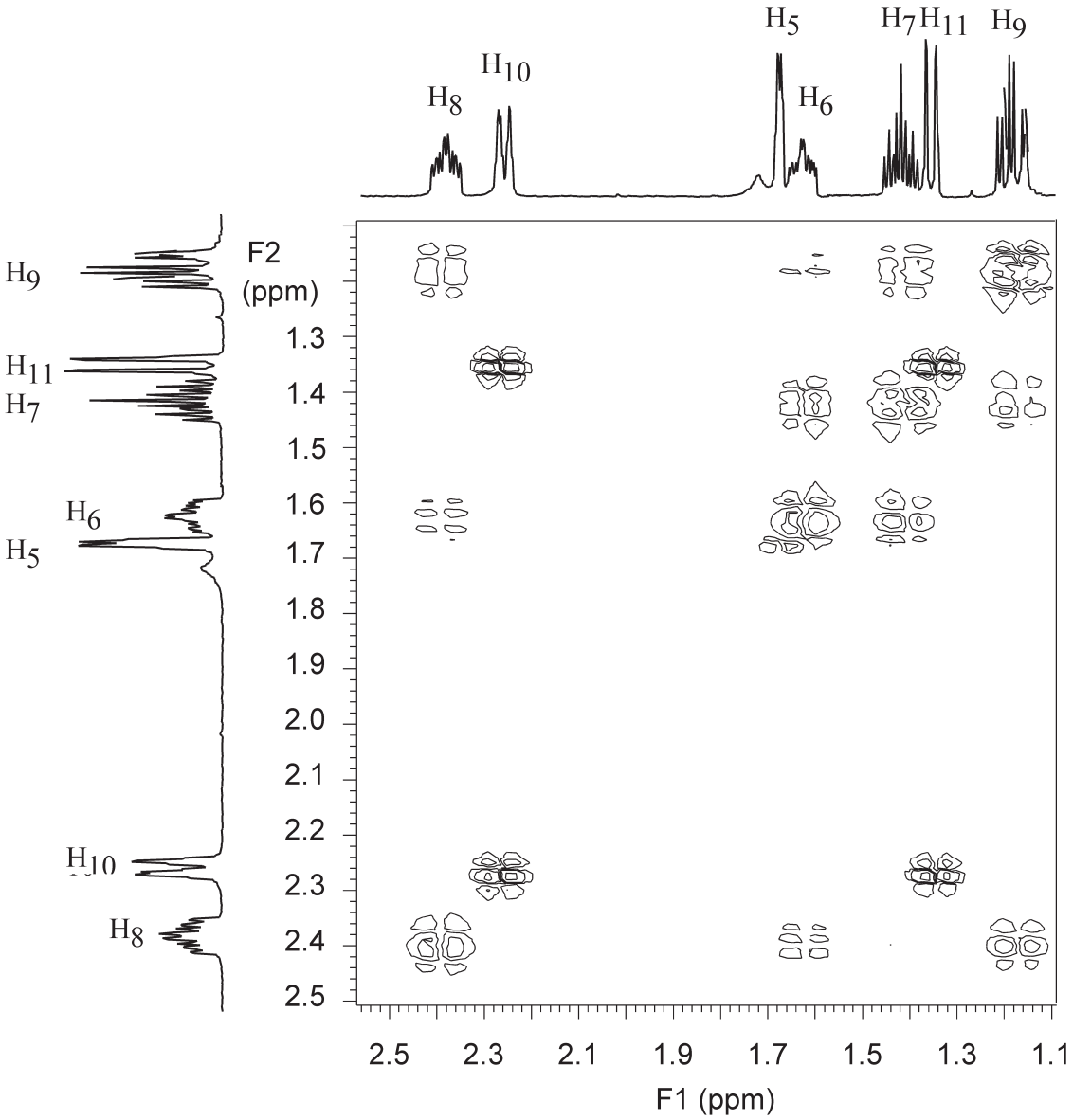


Figure 3.2 *COSY spectrum of* ***(-)-3.11f.***

From *HETCOR* spectra (not shown), the signal at δ 1.68 could be assigned to H_5 since it clearly belong to a CH-group. Furthermore, *HETCOR* gives three sets of signals for the three CH_2-groups of the fenchone moiety (δ 1.37 and 2.28; δ 1.20 and 2.40; δ 1.43 and 1.64). On the basis of the coupling constants of the signals at δ 1.37 and 2.28 in the ^{1}H NMR, the fact that they exhibited *COSY* interactions only with each other (Figure 3.2) and the *NOE*-correlation with H_5, we assigned these signals to the bridge protons (Figure 3.3).

The signal at δ 2.28 has *NOE* interactions with the signal at δ 1.37, one of the benzylic protons, H_5 and two of the methyl groups, and therefore we assigned this signal to H_{10}. The signal at δ 1.37 has interactions with H_{10} and the signal at δ 1.20, from one of the *exo*-protons H_9 or H_7. This *exo*-proton at δ 1.20 has a *COSY* and *HETCOR* correlation with the signal at δ 2.40, which arises from one of the *endo*-protons. Also a *COSY* with the signal at δ 1.43 is

observed, which corresponds to the other *exo*-proton. This leaves the signals at δ 1.64 for the other *endo* proton. The signal at δ 1.64 has an *NOE* interaction with the methyl group at δ 1.08, and therefore, it could be assigned as $H_{6,}$ and subsequently, the signal at δ 2.40 could be assigned as H_8.

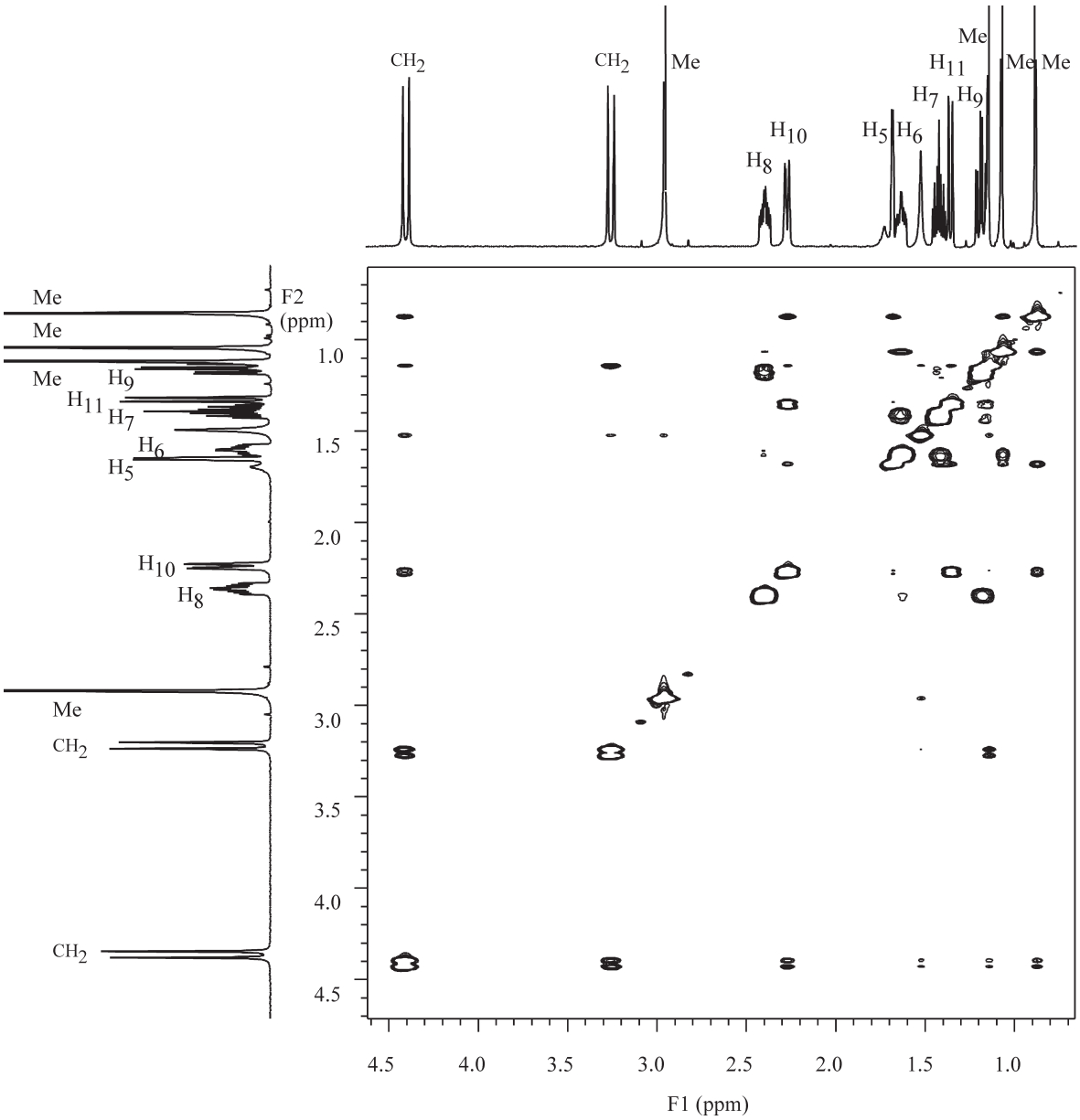


Figure 3.3 *NOESY spectrum of (-)-**3.11f**.*

The *exo* protons could now be assigned as H_7 and H_9 for the signals at δ 1.43 and 1.20, respectively. From the correlation of the bridge proton H_{10} with the benzylic protons, it is clear that addition has taken place from the *exo* side of the thioketone. It cannot be taken for granted that addition of a nucleophile will occur exclusively from the *exo* side. Although, for example, dissolving metal reductions of fenchone produce almost exclusively *endo* alcohol

(addition of hydride equivalent from the *exo* side),[11] we observed that addition of 2,6-lutidine (as the monolithio derivative) occurs roughly equally from the *exo* and *endo* sides.[12] On the other hand, 1,3-dipolar addition of diazo compounds to thiofenchone gives a single adduct thought to be *exo* addition product.[13]

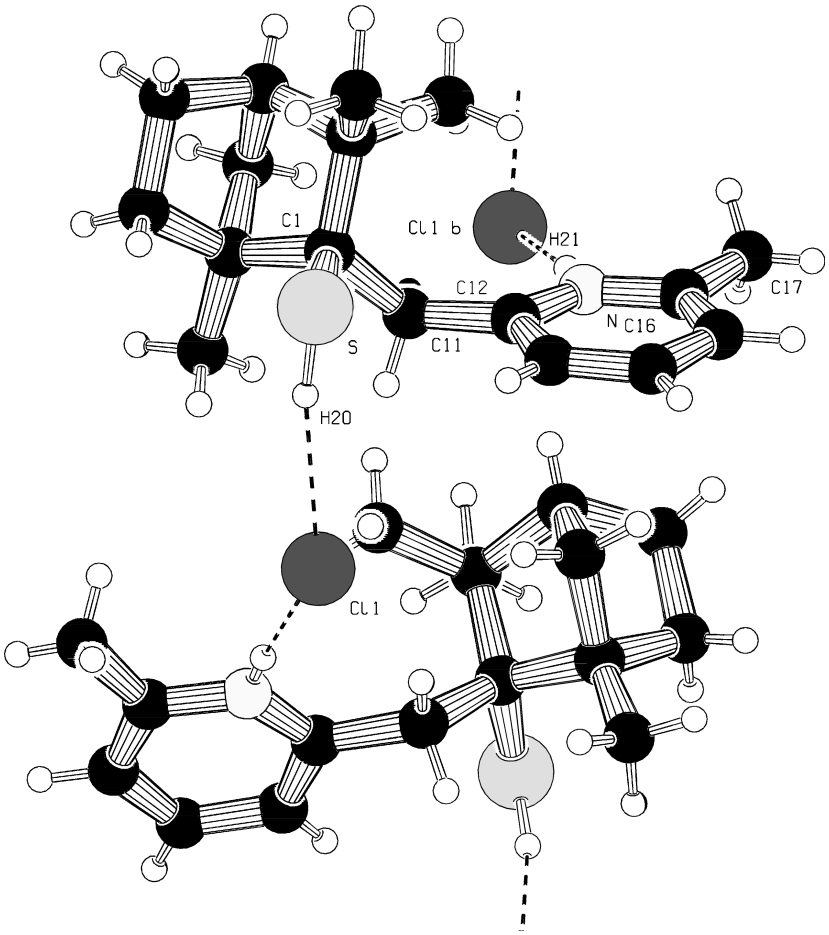
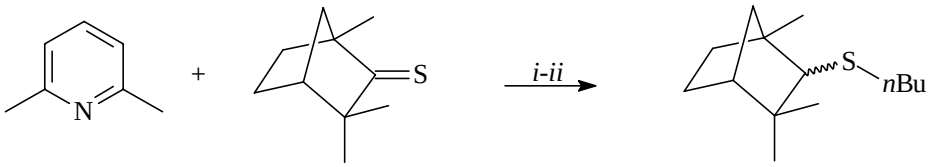


Figure 3.4 *X-ray structure of (–)-**3.11f**·HCl.*

By good fortune, we obtained satisfactory crystals and were able to confirm this structural assignment of the (–)-**3.11f**·HCl-complex by crystallographic means (Figure 3.4). The crystals easily lose HCl upon exposure to air and therefore had to be taken from the mother liquor. The packing diagram of the X-ray structure (not shown) reveals a polymeric chain with alternating HCl molecules and the ligand moiety. The proton of hydrogen chloride is coordinated to the pyridine nitrogen of one molecule, and the chlorine is coordinated to the thiol hydrogen of a second molecule. This unit is continuously repeated. The crystal structure of hydrochloric acid in solid argon also consists of polymeric strands.[14] Previous crystal structures of complexes with pyridine diols and dithiols (two arms instead of one) show encapsulation of monomeric hydrochloric acid into the cavity of these molecules, rather than the polymeric structure observed here.[15,2b]

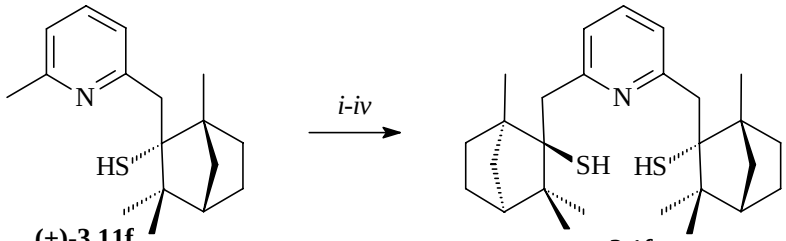
C-alkylation of thiofenchone with organolithium reagents cannot be taken for granted. When (*R*)-thiofenchone **3.13** and 2,6-lutidine **3.10** were dissolved in THF and allowed to react with *n*-butyllithium exclusive thiophilic addition of the *n*-butyl group occurred affording the thioether **3.14** (Scheme 3.7). The butyl group acts as nucleophile in this reaction and adds selectively to the sulfuratom. Under the reaction conditions used it is clear that the lutidine had not yet been lithiated. There is a fundamental difference in the behavior of lithiated methylpyridine and simple alkyllithium



3.10 **3.13** **3.14**

Scheme 3.7 *Reagents and conditions*: *i, n*-BuLi, -80°C; *ii* H_3O^+.

The monoadduct (+)-**3.11f** was further functionalized following the approach of Scheme 3.5. Addition of *n*-BuLi (2.2 equiv.) to a solution of the monoadduct (+)-**3.11f** in THF, followed by the addition of 1.1 equiv. of *(R)*-thiofenchone, led to the dithioladduct **3.1f** in 79% yield (Scheme 3.8).



(+)-3.11f **3.1f**

Scheme 3.8 *Reagents and conditions : i, n*-BuLi (2.1 equiv.), THF, –70 °C; *ii* – 70 °C→ –40 °C; *iii* (*R*)-thiofenchone; *iv* H_3O^+.

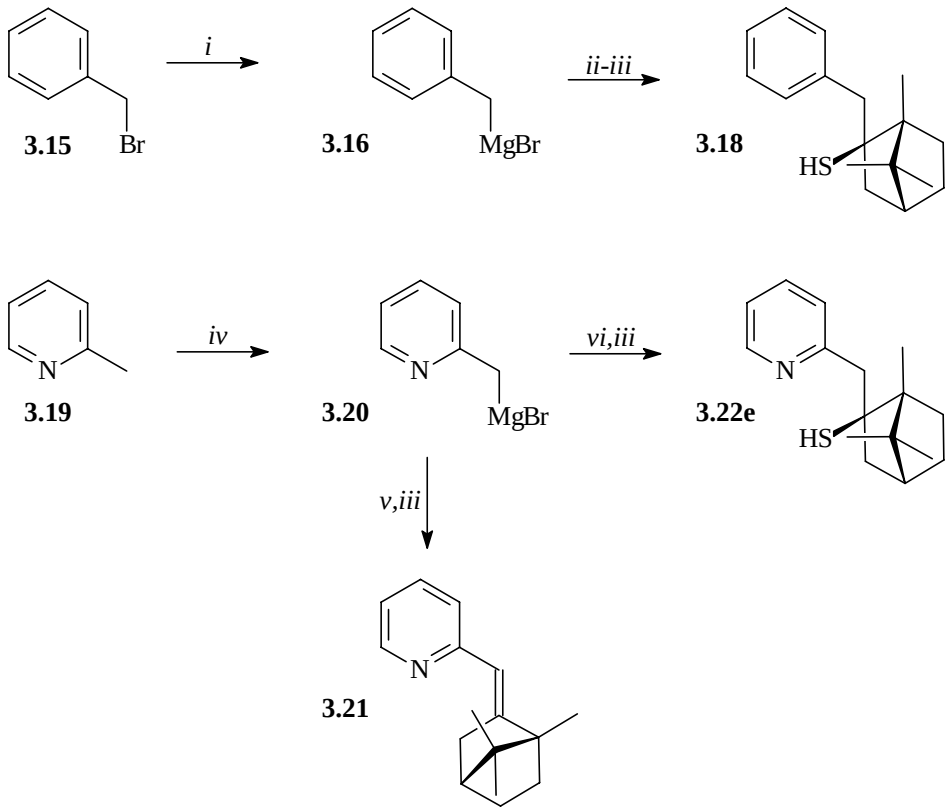
Formation of the C_s-symmetrical addition adduct, as was observed for the pyridine diols (**2.7**), did not take place. Addition cleanly took place at the less sterically hindered methyl group affording the C_2-symmetrical pyridine dithiol **3.1f.**

3.5 Thiocamphor adducts.

A drawback using the approach presented in Scheme 3.5 is the need for nonenolizable thioketones, which severely restricts the number of suitable thioketones. To broaden the scope of our direct approach less basic organomagnesium reagents were used to C-alkylate

the thioketones. When benzylbromide **3.15** was converted to the Grignard reagent **3.16** and allowed to react with (*R*)-thiocamphor **3.17** exclusive C-alkylation took place affording the thiol **3.18** in 40% yield. Addition to the thiocamphor carbon atom was found to be *endo*-selective. The low yield can be ascribed to enolization of the thiocamphor, the rate of which still competes with the rate of addition of benzylmagnesiumbromide. Using benzylmagnesiumchloride no product could be isolated at all. The orange color of the thioketone, however, disappears and reappears after hydrolysis indicating that enolization is the reason of failure. When benzylmagnesiumiodide is used the thiol **3.18** was isolated in 55% yield.

Formation of pyridine thiols based on (*R*)-thiocamphor was attempted though carbon-selective addition with Grignard reagent **3.20**, formed from 2-picoline **3.19** and EtMgBr. However when the reactions were performed in refluxing THF no pyridine thiol could be isolated, instead the pyridine alkene **3.21** was formed. This indicates that C-alkylation indeed takes place, however, it is followed by elimination of the sulfur atom. When the same procedure was followed at room temperature elimination of sulfur did not take place and the pyridine thiol **3.22e** could be isolated in 52 % yield. Again *endo* and C-selective addition had taken place.



Scheme 3.9 *Reagents and conditions : i*, Mg, Et_2O; *ii* (*R*)-thiocamphor, reflux; *iii* 2N NH_4Cl; *iv* EtMgBr, THF, reflux 4h; *v* (*R*)-thiocamphor, reflux; *vi* (*R*)-thiocamphor, rt.

3.6 Conclusions.

The base-induced addition of 2,6-lutidine **3.10** to achiral as well as chiral thioketones is a simple and direct approach to obtain pyridine dithiols **3.1**. This approach, however, is restricted to nonenolizable thioketones like thioadamantanone and thiofenchone since enolization can easily take place. Furthermore this approach is restricted to aliphatic thioketones because thiophilic addition is a severe side reaction when aromatic thioketones are used. The scope of the direct addition to thioketones can be extended to enolizable thioketones like thiocamphor by making use of pyridine magnesiumbromide **3.20**. Depending on the pyridine-metal reagent used a variety of pyridine thiols can be synthesized.

3.7 Experimental Section.

General Remarks: See Chapter 2. Thioadamantanone as well as (*R*)- and (*S*)-thiofenchone were prepared following literature procedures starting from adamantanone[9], (*R*)-(–)-fenchone and (*S*)-(+)-fenchone respectively.[16]

2-[(6-Methyl-2-pyridinyl)methyl]-2-adamantanethiol 3.11b

A solution of 2,6-lutidine **3.10** (7.5 g, 70 mmol) in 150 mL of dry THF was cooled to –50°C. After addition of *n*-butyllithium (1.6 M solution in hexane, 70 mmol, 44 mL) the orange colored solution was stirred at -20 °C for 1 hour. Subsequently, the mixture was cooled to –80°C and a solution of 2-thioadamantanone (14.0 g, 84 mmol) in 25 mL of THF was added dropwise. After stirring overnight at room temperature the dark brown reaction mixture was poured into 50 mL 2 N HCl solution and stirred for 30 min. The solution was neutralized and extracted three times with ethylacetate. The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent afforded 16 g. of crude product. This product can be used without purification for further synthesis. Alternatively bulb to bulb distillation (bp 170 °C, 0.1 mm Hg) followed by crystallization from hexane afforded **3.11b** as a colorless crystalline material (14.5 g, 53 mmol, 76%): mp 58-59°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62-2.45 (m, 14H), 2.54 (s, 3H), 3.10 (s, 1H), 3.37 (s, 2H), 7.04 (d, *J* = 11.97 Hz, 1H), 7.06 (d, *J* = 11.96 Hz, 1H), 7.44 (dd, *J* = 11.97 Hz, *J* = 11.96 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 24.54 (d), 27.09 (d), 27.56 (d), 33.56 (t), 34.39 (t), 38.32 (t), 39.24 (q), 47.56 (t), 56.66 (s), 120.90 (d), 122.12 (d), 135.94 (d), 157.34 (s), 158.03 (s); HRMS calcd 273.154, found 273.154. Anal. Calcd for $C_{17}H_{23}NS$: C, 74.67; H, 8.48; N, 5.12. Found: C, 74.49; H, 8.55; N, 5.17.

2-({6-[(2-Methyl-2-adamantyl)methyl]-2-pyridinyl}methyl)-2-adamantanethiol 3.1b

A solution of **3.11b** (5.46 g, 20 mmol) in 100 mL of dry THF was cooled to –70°C. After addition of *n*-butyllithium (1.6 M solution in hexane, 27 mL, 43.2 mmol) the orange colored solution was stirred at –40°C for 2 hours. Subsequently, the mixture was cooled to –70°C and a solution of 2-thioadamantanone (5.0 g, 30 mmol) in 20 mL of THF was added dropwise. Stirring was continued and the mixture was allowed to reach ambient temperature. After stirring overnight the dark red mixture was poured into 10 mL of 5N HCl solution and stirred for 30 min. The aqueous layer was neutralized and extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and taken to dryness. The residue was taken up in dry ether and filtered, yielding the crude product as a light brown solid. Crystallization from a dichloromethane/hexane mixture afforded **3.1b** as colorless needles (7.0 g, 16 mmol, 80%): mp 196-197°C; ^{1}H NMR (300 MHz, $CDC1_3$): δ 1.42-1.83 (m, 12 H), 1.88-1.96 (m, 8H), 2.41 (m, 8H), 2.62 (s, 2H), 3.38 (s, 4H), 7.15 (d, *J* = 7.69 Hz, 2H), 7.49 (dd, *J* = 7.69 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 27.13 (d), 27.59 (d), 33.58 (t), 34.31 (t), 38.28 (d), 39.26 (t), 47.99 (t), 56.82 (s), 123.36 (d), 135.30 (d), 1 58.04 (s); IR (KBr): 3430 (br), 2900 (s), 2665 (br), 2590 (br), 2460 (br), 1980 (br), 1630 (s), 1450 (s), 1340 (s), 1010 (s), 808 (s); HRMS calcd for $C_{27}H_{37}NS_2$: 439.237, found 439.237. Anal. Calcd for $C_{27}H_{37}NS_2$: C, 73.75; H, 8.48; N, 3.19. Found: C, 73.29; H, 8.44; N, 3.23

Crystal Structure of 3.1b

Crystal Data: Formula: $C_{27}H_{37}NS_2$, M = 439.73. Suitable transparent needle-shaped crystals of approximate size 0.08 x 0.12 x 0.5 mm were obtained by recrystallization from dichloromethane/hexane. orthorhombic, $P2_12_12_1$, *a* = 6.515(1), *b* = 10.668(1), *c* = 31.943(3) Å, V = 2220.1(5) Å , Z = 4, D_x = 1.316 g cm^{-1}, λ(MoK$\bar{\alpha}$) = 0.71073 Å, μ = 2.6 cm , F(000) = 952, T = 130 K. *Data collection:* The data were collected on an Enraf-Nonius *CAD-4F*^{2} diffractometer (Mo tube, 50 kV, 40 mA, monochromated Mo-K$\bar{\alpha}$ radiation, Δω = 1.05 + 0.34 tg θ), range 16.24° < θ < 20.15°. reflections collected: 5141 independent reflections: 4244. *Solutions and refinement*: The structure was solved by Patterson methods and extension of the model was accomplished by direct methods applied to difference structure factors using the program *DIRDIF*.[17] *wR*(F^2) = 0.115 for 4244 reflections with $F_o^2 \geq 0$ and *R*(*F*) = 0.046 for 3493 unique observed reflections with $F_o \geq 4.0\ \sigma(F_o)$ and 296 parameters.

Table 3.1 : *Interatomic distances and selected bond angles for compound **3.1b***

Interatomic Distances (Å)					
S(1)[a]	-C(7)	1.849(4)[b]	C(6)	-C(7)	1.550(5)
S(2)	-C(18)	1.851(3)	C(17)	-C(18)	1.551(5)
N(1)	-C(1)	1.345(5)	H(1')	-S(1)	1.301
N(1)	-C(5)	1.347(5)	H(2')	-S(2)	1.297
C(1)	-C(6)	1.513(5)	H(1')	-N(1)	3.151
C(5)	-C(17)	1.504(5)	H(2')	-N(1)	3.350

Bond angles (deg.)							
C(1)	-N(1)	-C(5)	117.8(3)	C(6)	-C(7)	-C(14)	109.3(3)
N(1)	-C(1)	-C(2)	122.2(3)	C(5)	-C(17)	-C(18)	117.1(3)
N(1)	-C(1)	-C(6)	116.5(3)	S(2)	-C(18)	-C(17)	106.8(2)
C(2)	-C(1)	-C(6)	121.3(3)	S(2)	-C(18)	-C(19)	107.0(2)
N(1)	-C(5)	-C(4)	122.5(3)	S(2)	-C(18)	-C(25)	111.3(2)
N(1)	-C(5)	-C(17)	117.2(3)	C(17)	-C(18)	-C(19)	109.6(3)
C(4)	-C(5)	-C(17)	120.2(3)	C(17)	-C(18)	-C(25)	114.4(3)
C(1)	-C(6)	-C(7)	118.0(3)	H(1')	-S(1)	-C(7)	109.34
S(1)	-C(7)	-C(6)	106.7(2)	H(2')	-S(2)	-C(18)	109.51
S(1)	-C(7)	-C(8)	110.9(2)	S(1)	-H(1')	-N(1)	108.09
S(1)	-C(7)	-C(14)	108.0(2)	S(2)	-H(2')	-N(1)	104.41
C(6)	-C(7)	-C(8)	113.9(3)				

[a] The numbering for the crystal data does not follow the numbering used in nomenclature.

[b] Standard deviation in parentheses.

(1*S*,2*S*)-1,3,3-Trimethyl-2-[(6-methyl-2-pyridinyl)methyl]bicyclo[2.2.1]heptane-2-thiol (–)-**3.11f.** To a solution of 2,6-lutidine **3.10** (0.35 g, 3.3 mmol) in 50 mL of THF at –60 °C was added *n*-butyllithium (1.6 M in hexane, 2.1 mL, 3.4 mmol). The mixture was stirred for 1 h at –40 °C and cooled to –60 °C again. A solution of (*S*)-thiofenchone (0.56 g, 3.3 mmol) in 5 mL of THF was added, and the mixture was stirred at –60 °C for 1 h. The cooling bath was removed, and the mixture was allowed to stir at ambient temperature overnight. The mixture was poured into 15 mL of 5 N HCl and stirred for 1 h before being neutralized with 2 N NaOH. The mixture was extracted three times with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by means of Kugelrohr distillation (135 °C; 2.0 mmHg), yielding a colorless solid (0.81 g, 2.9 mmol, 89%): mp 113-114 °C; $[\alpha]^{23}_D$ –87.5 (*c* 3.6, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (s, 3H), 1.15 (m, 2H), 1.19 (s, 3H), 1.26 (s, 3H), 1.40 (m, 1H), 1.64 (m, 1H), 1.76 (m, 1H), 1.93 (m, 1H), 2.19 (m, 1H), 2.52 (s, 3H), 3.30 (s, 2H), 4.67 (br, SH), 6.92 (d, *J* = 7.63 Hz, 1H),

7.06 (d, *J* = 7.93 Hz, 1H), 7.42 (dd, *J* = 7.63 Hz, *J* = 7.93 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 18.19 (q), 24.38 (t), 27.31 (q), 28.79 (q), 33.62 (t), 40.27 (t), 45.54 (s), 47.89 (t), 50.85 (d), 54.37 (s), 62.34 (s), 119.80 (d), 121.47 (d), 136.03 (d), 156.20 (s), 161.15 (s); HRMS calcd. 275.171, found 275.171. Anal. Calcd. for $C_{17}H_{25}NS$: C, 74.13; H, 9.15; N, 5.08. Found C, 74.10; H, 9.11; N, 5.10.

(1*R*,2*R*)-1,3,3-Trimethyl-2-[(6-methyl-2-pyridinyl)methyl]bicyclo[2.2.1]heptane-2-thiol ((+)-**3.11f).** This compound was prepared using the same procedure as for (–)-**3.11f** starting from 2,6-lutidine **3.10** and S-thiofenchone, affording (+)-**3.11f** in comparable yields: mp 114-115 °C; $[\alpha]^{23}_D$ +85.8 (*c* 3.6, methanol).

(1*S*,2*S*)-1,3,3-Trimethyl-2-[(6-methyl-2-pyridinyl)methyl]bicyclo[2.2.1]heptane-2-thiol. HCl ((–)-**3.11f·HCl).** A solution of the monoadduct (–)-**3.11f** (0.25 g, 0.91 mmol) in dichloromethane (10 mL) was passed through a stream of HCl for 2 min. The mixture was stirred for 2 h and the solvent was carefully evaporated at reduced pressure to yield the crude HCl complex, which was recrystallized from hexane/dichloromethane (0.27 g, 0.87 mmol, 95%): mp 181-182 °C; $[\alpha]^{23}_D$ =–62.1 (*c* 2.9, chloroform); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.08 (s, 3H), 1.16 (s, 3H), 1.20 (m, 1H), 1.37 (d, *J* = 10.99 Hz, 1H), 1.43 (m, 1H), 1.52 (s, SH), 1.64 (m, 1H), 1.69 (m, 1H), 2.28 (d, *J* = 10.99 Hz, 1H), 2.40 (m, 1H), 2.98 (s, 3H), 3.26 (d, *J* = 17.2 Hz, 1H), 4.43 (d, *J* = 17.2 Hz, 1H), 7.42 (d, *J* = 7.69 Hz, 1H), 8.09 (dd, *J* = 8.05 Hz, *J* = 7.69 Hz, 1H), 8.80 (d, *J* = 8.05 Hz, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 17.65 (q), 24.44 (t), 26.07 (q), 29.39 (q), 33.68 (t), 40.20 (t), 44.44 (t), 45.31 (s), 50.68 (d), 56.15 (s), 63.29 (s), 124.39 (d), 124.83 (d), 143.09 (d), 153.48 (s), 157.91 (s); HRMS calcd. 311.147, found 275.171 (-HCl). Anal. Calcd. for $C_{17}H_{26}NSCl$: C, 65.46; H, 8.40; N, 4.49, Cl, 11.37. Found C, 65.16; H, 8.22; N, 4.42, Cl, 11.38.

Crystal Structure of (–)-3.11f.HCl

Crystal Data: Formula: $[C_{17}H_{26}ClNS]^+.Cl^-.CH_2Cl_2$, M = 396.85, The crystal, used for characterization and data collection, was irregular and block-shaped of approximate size 0.20 x 0.25 x 0.37 mm. The crystal was selected from the mother liquid: outside the liquid the crystal lost HCl. The crystal was orthorhombic, $P2_12_12_1$, *a* = 10.425(1), *b* = 11.075(2), *c* = 17.230(3) Å, *V* = 1989.3(5) Å, *Z* = 4, D_x = 1.325 g cm^{-1}, μ = 5.65 cm , *F*(000) = 840. *Data collection*: The data were collected on an Enraf-Nonius *CAD-4F* diffractometer (Mo tube, 50 kV, 40 mA, monochromated Mo-Kα radiation, Δω = 0.90 + 0.34 tg θ); T = 130 K, range 1.18° < θ < 27.0°, reflections collected*:* 4709 independent reflections 4258. *Solutions and refinement*: The structure was solved by Patterson methods and extension of the model was accomplished by direct methods applied to difference structure factors using the program *DIRDIF*. Refined anisotropically by full-matrix least squares based on F^2 (SHELXL);

data/parameters 4258/320 ; $R(F)$ = 0.0301 [$F_o \geq 4.0\ \sigma(F_o)$], $wR(F^2)$ = 0.0739 [$F^2>0$]; absolute-structure parameters; maximal residual electron density (±0.39(5) e/Å^3). The program PLUTO has been used for graphical representations of the crystal structure.

Table 3.2 : *Interatomic distances and selected bond angles for compound **(–)-3.11f**.HCl*

Interatomic Distances (Å)					
S(1)[a]	-C(1)	1.8429(18)[b]	C(1)	-C(11)	1.557(3)
N(1)	-C(12)	1.347(2)	H(20)	-S(1)	1.26(3)
N(1)	-C(16)	1.347(3)	H(20)	-Cl(1)	2.48(3)
C(1)	-C(2)	1.580(3)	H(21)	-Cl(1)	2.31(3)
C(1)	-C(5)	1.609(3)	H(21)	-N(1)	0.76(3)

Bond angles (deg.)							
C(12)	-N(1)	-C(16)	125.48(17)	C(11)	-C(12)	-C(13)	126.22(17)
S(1)	-C(1)	-C(2)	113.07(13)	N(1)	-C(16)	-C(15)	118.13(18)
S(1)	-C(1)	-C(5)	110.36(11)	N(1)	-C(16)	-C(17)	117.9(2)
S(1)	-C(1)	-C(11)	107.85(12)	C(15)	-C(16)	-C(17)	124.0(2)
C(2)	-C(1)	-C(5)	101.96(14)	H(20)	-S(1)	-C(1)	96.3(15)
C(2)	-C(1)	-C(11)	107.38(14)	S(1)	-H(20)	-Cl(1)	170(2)
C(5)	-C(1)	-C(11)	116.24(15)	N(1)	-H(21)	-Cl(1)	171(2)
N(1)	-C(12)	-C(11)	116.59(16)	H(21)	-N(1)	-C(12)	119(2)
N(1)	-C(12)	-C(13)	116.78(17)	H(21)	-N(1)	-C(16)	115(2)

[a] The numbering for the crystal data does not follow the numbering used in nomenclature.

[b] Standard deviation in parentheses.

(1*S*,2*S*)-1,3,3-Trimethyl-2-[(6-{[(1*S*,2*S*)-1,3,3-trimethyl-2-sulfanylbicyclo[2.2.1]hept-2-yl]methyl}-2-pyridinyl)methyl]bicyclo[2.2.1]heptane-2-thiol (3.1f). To a solution of (+)-**3.11f** (0.29 g, 1.05 mmol) in 50 mL of THF at –70 °C was added *n*-butyllithium (1.6 M in hexane, 1.4 mL, 2.2 mmol). The mixture was stirred for 90 min at –40 °C and cooled to –70 °C again. A solution of (*R*)-thiofenchone (0.20 g, 1.19 mmol) in 5 mL of THF was added, and the mixture was stirred at –70 °C for 1 h. The cooling bath was removed, and the mixture was allowed to stir at ambient temperature overnight. The mixture was poured into 15 mL of 5 N HCl solution and stirred for 1 h before it was neutralized with a 2 N NaOH solution. The mixture was extracted three times with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by means of column chromatography (silica gel, hexane/dichloromethane (2:1)) yielding **3.1f** as a colorless solid (0.37 g, 0.83 mmol, 79%): mp 139-140 °C; $[\alpha]^{23}_D$ –80 (*c* 4.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 6H), 1.15 (m, 2H), 1.16 (s, 6H) 1.20 (s, 6H), 1.23 (d, *J* = 10.5 Hz, 2H), 1.41

(m, 2H), 1.65 (d, *J* = 4.4 Hz, 2H), 1.73 (m, 2H), 1.97 (d, *J* = 10.5 Hz, 2H), 2.26 (d, *J* = 16.6 Hz, 2H), 2.28 (m, 2H), 3.35 (d, *J* = 16.6 Hz, 2H), 3.36 (s, 2SH), 7.46 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 18.15 (q), 24.65 (t), 27.39 (q), 29.34 (q), 33.79 (t), 40.30 (t), 45.44 (s), 49.18 (t), 51.02 (d), 55.08 (s), 62.74 (s), 121.57 (d), 135.54 (d), 169.24 (s); HRMS calcd. 443.268, found 443.268. Anal. Calcd. for $C_{27}H_{41}NS_2$: C, 73.08; H, 9.31; N, 3.16. Found C, 73.08; H, 9.31; N, 3.15.

(*R*)-Thiocamphor 3.17

To a stirred solution of (*R*)-camphor (11.0 g, 72.4 mmol) in 300 mL of toluene was added Lawesson's reagent (29.2 g, 72.4 mmol) and the mixture was refluxed overnight. After removal of the solvent in vacuo the product was flushed over a column of silica with diethyl ether. The product was purified by sublimation (80 °C, 5.0 mm Hg) yielding **3.17** as an orange solid (10.3 g, 61.5 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73 m (s, 3H), 0.97 (s, 3H), 1.04 (s, 3H), 1.27 (m, 2H), 1.69 (m, 1H), 1.93 (m, 1H), 2.11 (m, 1H), 2.35 (d, *J* = 20.5 Hz, 1H), 2.72 (m, 1H). All other spectroscopic data were in accordance to literature.[16]

(1*R*,2*R*)-2-benzyl-1,7,7-trimethylbicyclo[2.2.1]heptane-2-thiol 3.18

A solution of benzylbromide **3.15** (1.0 g, 5.8 mmol) in 10 mL of diethyl ether was added to magnesium (0.14 g, 6.0 mmol) and refluxed for 1 h. (*R*)-thiocamphor **3.17** (0.67 g, 4.0 mmol) in 10 mL of diethyl ether was added and the mixture was refluxed overnight. 10 mL of 2N NH_4Cl was added and the layers were separated. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine and dried over Na_2SO_4. The product **3.18** was purified by means of column chromatography (silica, diethyl ether/hexane (1:2)) yielding a colorless oil (0.41g, 1.6 mmol, 40%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (s, 3H), 0.89 (s, 3H), 1.06 (s, 3H) 1.21 (m, 1H), 1.40 (m, 1H), 1.81 (m, 2H), 2.00 (m, 1H), 2.12 (br, SH), 2.47 (d, *J* = 20.5 Hz, 1H), 2.93 (m, 1H), 4.62 (s, 2H), 7.29 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.97 (q), 18.11 (q), 19.15 (q), 26.86 (t), 35.79 (t), 35.81 (t), 38.05 (t), 44.17 (d), 50.09 (s), 56.08 (s), 64.12 (s), 65.11 (t), 126.82 (d), 127.43 (d), 128.37 (d), 140.80 (s). HRMS calcd.260.160, found 260.161. Anal. Calcd. for $C_{17}H_{24}S$: C, 78.40; H, 9.29; S, 12.31; Found C, 78.21; H, 9.35; S, 12.15.

2-[(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylidene)methyl]pyridine 3.21

Following a literature procedure 2-picoline **3.19** (0.8 g, 8.6 mmol) was converted with ethylmagnesiumbromide to the Grignard reagent **3.20** and was used as such.[18] To a solution of Grignard reagent **3.20** in THF was added (*R*)-thiocamphor **3.17** (0.84 g, 5.0 mmol) and the mixture was refluxed overnight. NH_4Cl was the mixture was extracted with ethyl acetate twice. The organic layers were washed with brine and dried over Na_2SO_4. Column chromatography (silica, hexane/diethyl ether (3:1)) afforded **3.21** as a colorless oil (0.52 g,

2.3 mmol, 45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (s, 3H), 0.89 (s, 3H), 1.01 (s, 3H) 1.19 (m, 2H), 1.30 (m, 1H), 1.71 (m, 2H), 1.84 (m, 1H), 2.36 (d, *J* = 18.7 Hz, 1H), 2.74 (m, 1H), 6.20 (s, 1H), 6.95 (m, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.51 (dd, *J* = 7.7 Hz, *J* = 7.7 Hz, 1H), 8.49 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 12.96 (q), 18.91 (q), 19.61 (q), 27.62 (t), 34.64 (t), 38.09 (t), 42.90 (d), 47.59 (s), 53.01 (s), 117.42 (d), 119.87 (d), 122.31 (d), 135.66 (d), 149.17 (d), 156.9 (s), 157.9 (s). HRMS calcd. 227.167, found 227.167. Anal. Calcd. for $C_{27}H_{41}NS_2$: C, 84.53; H, 9.31; N, 6.16. Found C, 84.15; H, 9.45; N, 5.99.

(2*R*)-1,7,7-trimethyl-2-(2-pyridinylmethyl)bicyclo[2.2.1]heptane-2-thiol 3.22e

2-picoline **3.19** (1.4 g, 15.0 mmol) was converted to the Grignard reagent **3.20** as described for **3.21** and (*R*)-thiocamphor **3.17** (2.0 g, 11.9 mmol) was added at room temperature. Stirring was continued overnight, NH_4Cl was added and the mixture was extracted twice with ethyl acetate. The organic layers were dried over Na_2SO_4. Column chromatography (silica, hexane/diethyl ether (5:1)) afforded **3.22e** as a colorless oil (1.6 g, 6.1 mmol, 52%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.86 (s, 3H), 1.11 (s, 3H) 1.20 (m, 1H), 1.50 (m, 1H), 1.72 (m, 2H), 1.92 (m, 1H), 2.11 (s, 2H), 2.43 (s, SH), 3.10 (dd, J = 13.19 Hz, J = 57.12 Hz, 2H), 7.07 (m, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.50 (t, *J* = 5.9 Hz, 1H), 8.49 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.21 (q), 21.48 (q), 22.40 (q), 26.87 (t), 31.37 (t), 45.87 (d), 47.31 (t), 50.00 (s), 50.45 (t), 53.49 (s), 55.95 (s), 121.24 (d), 125.70 (d), 135.43 (d), 148.49 (d), 159.98 (s). HRMS calcd. 261.155, found 261.156. Anal. Calcd. for $C_{16}H_{23}NS$: C, 73.51 H, 8.87; N, 5.36. Found C, 73.83; H, 8.95; N, 5.44.

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CHAPTER 4

Complexation of Pyridine Alcohols and Thiols.*

Abstract: Complexes of the pyridine diols **2.1** and dithiols **3.1** with protic acids as well as zinc salt were investigated. HCl complexes were formed with pyridine dithiol **3.1b**, pyridine diols **2.1d** and **2.7b**. The complex **3.1b**·HCl lost HCl from the solid under reduced pressure. This remarkable physical property suggests complexation of covalent HCl. On the other hand X-ray diffraction, ^{1}H NMR data and IR spectroscopy all point, however, to an ionic character of the HCl bond. Complexes of diol **2.1b** and thiols **3.1b** and **3.11f** with HBr were also prepared. Addition of the HCl and HBr complexes to cyclohexene oxide **4.1a** or cyclopentene oxide **4.1b** afforded the corresponding chloro- and bromohydrins. No reproducible enantioselection was observed when chiral complexes were used. Complexation of HNO_3 with pyridine diol **2.1b** afforded the acid complex. With pyridine dithiol **3.1b** a complex with HNO_3 could be prepared at 0 °C. Complex formation at room temperature gave rise to oxidation of the thiol groups. Zinc complexes of the pyridine diols **2.1** were easily prepared. Complexation of pyridine dithiol **3.1b** with $Zn(NO_3)_2$ gave the dimeric zinc complex **4.4b**. Complexation with $ZnCl_2$ gave rise to 28% of the dimeric zinc complex **4.4b** and for 60% a complex of HCL·$ZnCl_2$·ROH with dithiol **3.1b** was obtained as established by X-ray diffraction. Complexation of **3.1f** with $Zn(NO_3)_2$ afforded the monomeric zinc complex **4.5f**.

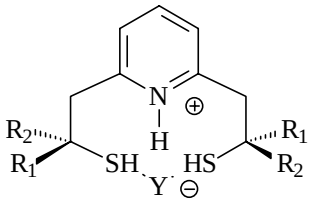
4.1 Introduction.

Previous research on pyridine diol **2.1b** revealed a high affinity of this tridentate ligand for the complexation of HCl.[1] It was found that the host organizes itself so that the acid is perfectly enclosed in a cavity wherein Cl is hydrogen bonded to the two hydroxyl groups and the proton of HCl is directed towards the pyridine nitrogen. In order to investigate the affinity of the pyridine diols **2.1** and dithiols **3.1** for acids and to study the self-organization of the cavity of these molecules various complexes of these ligands were prepared and studied with X-ray diffraction.

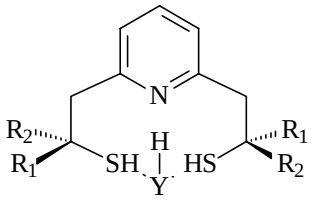
4.2 Complexes with Acids.

4.2.1 Complexation of HCl.

To obtain complex **3.1b**·HCl the tridentate pyridine dithiol **3.1b** was allowed to react with one equivalent of HCl using a freshly prepared titrated solution of HCl in chloroform. It is also possible to use HCl gas in excess for the complex formation, although a complication is slow elimination of H_2S affording the mono and di-olefins as indicated by ^{1}H NMR. The ^{1}H NMR of the complex **3.1b**·HCl shows remarkable differences compared to the free ligand **3.1b** indicating substantial differences in solution. A downfield shift of the signal from the benzylic protons (0.66 ppm) and increased complexity of the signals from the protons of the adamantyl moiety compared to the free ligand are observed. Also a large downfield shift of the pyridine protons is observed (0.62 ppm for 4-hydrogen and 0.29 ppm for 3- and 5-hydrogen) indicating that protonation of the nitrogen has taken place. This seems to be a general indication of protonation of pyridine diols and dithiols.



Formulation A



Formulation B

The large chemical shifts of the pyridine protons in the ^{1}H NMR on complexation of HCl are consistent with a complex that consists of a tight ion pair (formulation A) rather than covalent HCl (formulation B). However, upon drying of the HCl-complex under high vacuum at room temperature we observed that HCl evaporates from the complex and free ligand **3.1b** is obtained. This is not observed for other complexes, for example 2,6-lutidine·HCl. This physical property would be consistent with a covalent HCl (formulation B). IR spectra of

3.1b·HCl in KBr are complicated by the fact that the HCl absorptions are hidden under the strong adamantyl C-H bands. This led us to the study of the DCl complex. In some cases the **3.1b**.DCl complex shows a sharp absorption at 2211 cm^{-1}, which is partially masked by a broad pyridine-D^+ absorption in the region 2212 to 1850 cm^{-1}. The 2211 cm^{-1} absorption is close to that expected for *covalent* D-Cl. For example, values of 2091 cm^{-1} and 2090 cm^{-1} for monomeric DCl in, respectively, the gas phase[2] and in an Ar matrix[3] are given in the recent literature. The ^{1}H NMR spectra as well as the infrared spectra indicate clearly that D-Cl has not exchanged with S-H (attempts to prepare the S-D derivative of **3.1b** have been unsuccessful owing to the failure of the S-H groups to exchange with D at a measurable rate either in free **3.1b** under neutral conditions or in the D-Cl complex). The 2211 cm^{-1} absorption is not observed in the D-Cl complex with 2,6-lutidine.

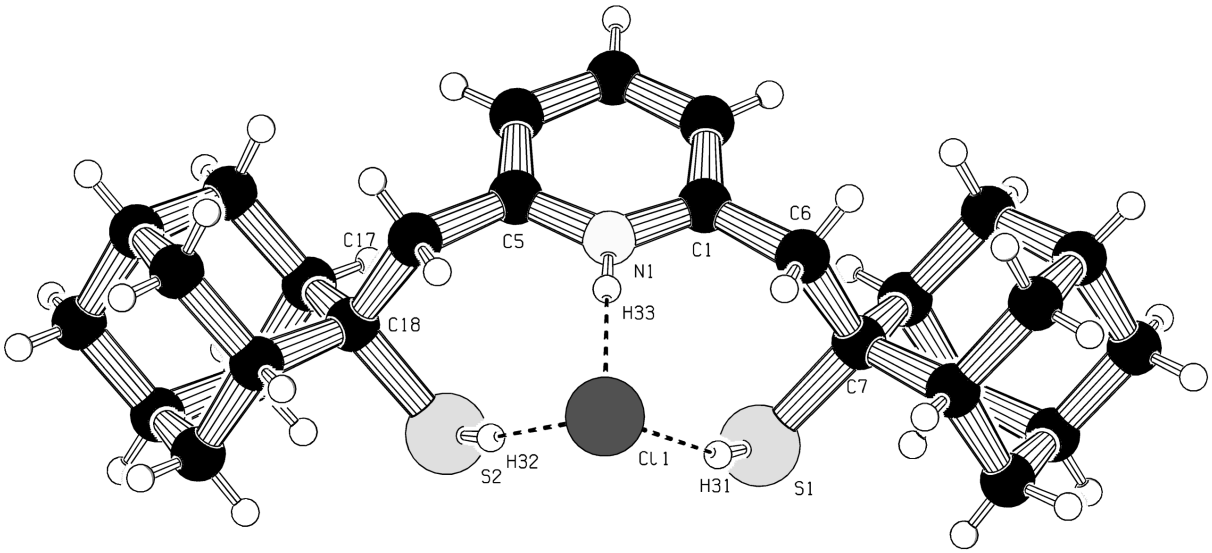


Figure 4.1 *Crystal structure of **3.1b**·HCl.*

More information of this complex was obtained from the crystal structure of the complex **3.1b**·HCl (Figure 4.1). Monomeric HCl is firmly embedded in a cavity and held in place by bonding to the pyridine nitrogen and the two thiols. The free pyridine dithiol **3.1b** (see Figure 3.1) is not preorganized in this arrangement. In the complex the thiol groups are clearly hydrogen bonded to the chloride although the bonds are unequal [H(31)...Cl(1) 2.58(3) Å; H(32)...Cl(1) 2.45(5) Å] likely the result of crystal packing effects, since in the ^{1}H NMR no differences can be found between the benzylic protons. The thiol groups bind from the same face (roughly a plane of symmetry in the complex).[3a] The H...Cl bond distance in **3.1b**·HCl is 2.19 Å, which is 0.92 Å longer than the covalent HCl bond length in the gas phase (1.27 Å).[4] A search of the Cambridge Data Base for pyridine...HCl complexes revealed an average bond length for the H...Cl bond distances of 2.20 Å with a deviation of 0.17 Å for 39 hits. For this screening a minimum N..H..Cl bond angle of 120° was included. Based on

these data and our experimental data we conclude that the HCl complex has an ionic character. However, the physical characterization of the complex suggest that transition to a more weakly bound form involving covalent HCl might be relatively easy.

The HCl complex of pyridine diol **2.1e** was prepared by passing through an excess of HCl. No elimination of water was observed. In the ^{1}H NMR spectrum large downfield chemical shifts for the pyridine protons were observed (0.55 ppm for the 4-hydrogen; 0.39 ppm for the 3- and 5-hydrogen), indicating a protonation of the nitrogen. Downfield shifts for the benzylic protons (0.38 ppm) were also observed. Furthermore they gave rise to a set of four signals all belonging to the same CH_2 groups the protons of which have now become nonequivalent. Probably due to the limited rotation on the NMR time scale the benzylic protons of **2.1e**·HCl have become diastereotopic. Apparently the structure of the complex has a locked conformation on the NMR time scale, whereas the free ligand **2.1e** has free rotation. X-ray analysis of the complex **2.1e**·HCl in comparison with the X-ray analysis of the free ligand **2.1e** (see Figure 2.2) revealed some remarkable differences. The molecular structure of **2.1e** shows an open C_2-symmetrical conformation of the ligand. The nitrogen forms strong intramolecular hydrogen bonds with the hydroxyl groups of the camphor moiety (H(61)…N(1) = 2.02(4), O(1)…H(61) = 0.84(4), H(62)…N(1) = 2.11(4), O(2)…H(62) = 0.79(4) Å) and is in this arrangement preorganized for complexation. In the X-ray analysis of **2.1b** only one of the hydroxyl groups forms a H-bond with the nitrogen of the pyridine ring and the other hydroxyl group forms a H-bond with the first hydroxyl group.[5]

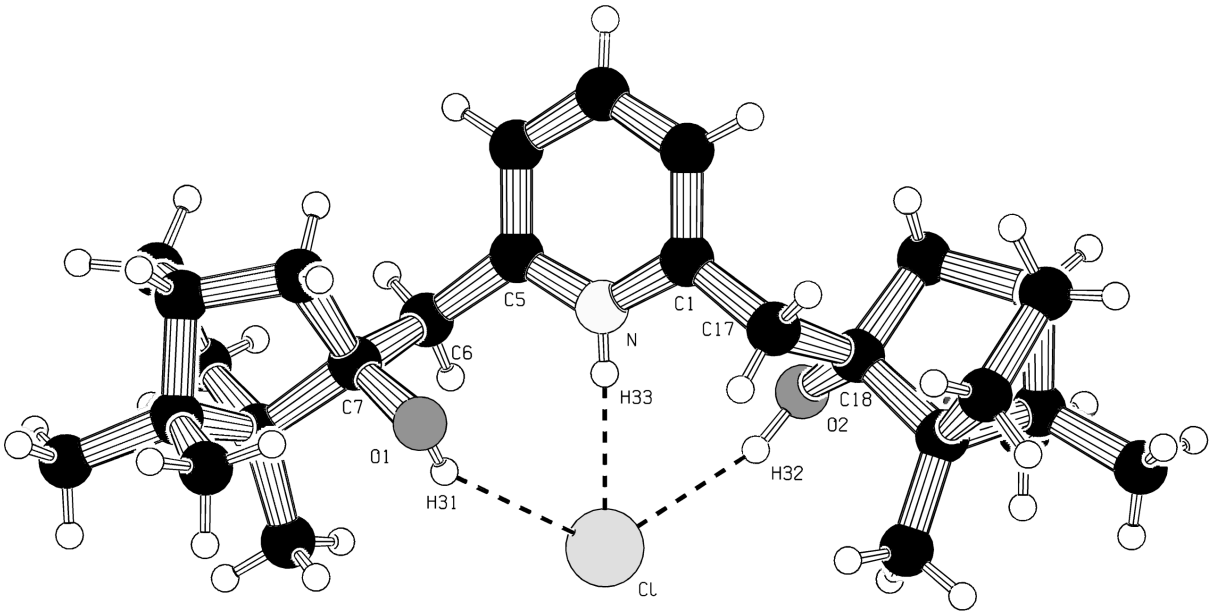


Figure 4.2 *Crystal structure of **2.1e**·HCl.*

The X-ray structure of complex **2.1e**·HCl (Figure 4.2) shows that the hydrogen chloride is firmly embedded in a cavity and held in place by bonding to the pyridine nitrogen and to the

hydroxyl groups. The hydroxyl groups are clearly hydrogen bonded to the chloride (H(31)…Cl(1) = 0.79(4), H(32)…Cl(1) = 0.97(4) Å). The bonds though are not of an equal length which is probably a result of the crystal packing effects. The pyridine nitrogen forms a strong bond with the hydrogen of acid (N(1)…H(33) = 0.85(4) Å) and the distance between the chloride and the hydrogen suggests an ionic character of the encapsulated acid (Cl(1)…H(33) = 2.23(4) Å).

Complexation of HCl with the C_s-symmetrical pyridine diol **2.7b** was also found to be possible. Again large downfield shifts for the pyridine protons are observed. Whether both hydroxyl groups of the ligand **2.7b** are involved in the binding of the HCl cannot be concluded from the spectral data. X-ray analysis of this complex, however, gave satisfactory evidence that only one hydroxyl group is involved (Figure 4.3). The crystal consisted of two independent asymmetric units, which each contains two anions, two chloride cations and one solvent dichloromethane molecule. Both units show hydrogen bonding between the chloride anion and one of the hydroxyl groups (O(2)-H(102)…Cl(3) = 2.18(3) Å) and the proton at the pyridine nitrogen (N(1)-H(111)…Cl(3) = 2.36(3) Å for unit 1, and O(3)-H(103)…Cl(4) = 2.27(3) Å, N(2)-H(112)…Cl(4) = 2.38(3) Å for unit 2). The hydroxyl group that does not form a hydrogen bond with the chloride is hydrogen bonded to the other hydroxyl group of the same molecule (O(1)…H(102) 2.03(4) Å for unit 1 and O(3)…H(104) 1.94(4) Å for unit 2). Although the HCl complex of **3.11f** (Figure 3.3) consists of a polymeric strain this HCl complex is monomeric.

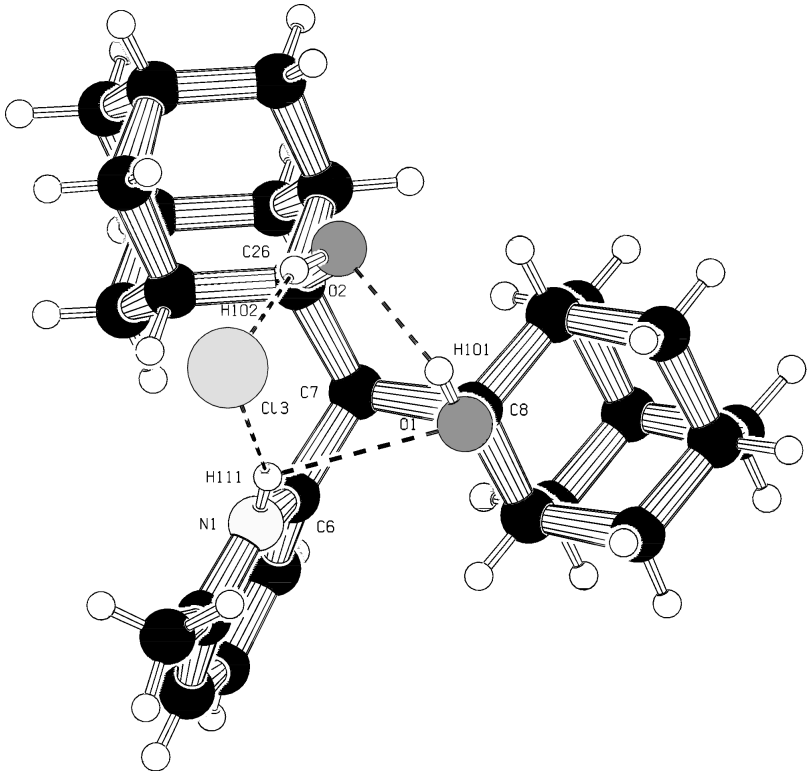


Figure 4.3 *Crystal structure of unit 1 of **2.7b**·HCl.*

4.2.2 Complexation of HBr and Nitric Acid.

Beside the complexation of HCl with these ligands the complexation of HBr was also possible. Complexes of **2.1b**, **3.11f**, and **3.1b** were prepared by slowly passing HBr through a solution of the free ligand in chloroform at 0°C. ^{1}H NMR of all complexes showed the protonation of the pyridine nitrogen. Again downfield shifts for the benzylic protons were observed. The ^{1}H NMR of **3.11f**·HCl, furthermore, shows a set of 4 signals for the benzylic protons indicating a locked conformation on NMR scale as was also seen for the HCl complex of **3.11f**.

Complexation of HNO_3 was also found to be successful. The complex of HNO_3 with pyridine diol **2.1b** was prepared by adding a HNO_3 solution (57%) to a solution of the free ligand. The product could be isolated after concentration and recrystallization from methanol. The HNO_3 complex of pyridine thiol **3.1b** was more troublesome due to the fact that the thiol groups are partly oxidized by the HNO_3 at ambient temperature. Complexation at 0°C, however, afforded the **3.1b**·HNO_3 complex. Suitable crystals for X-ray diffraction of the complex **3.1b**·HNO_3 could be obtained from chloroform/hexane (Figure 4.4).

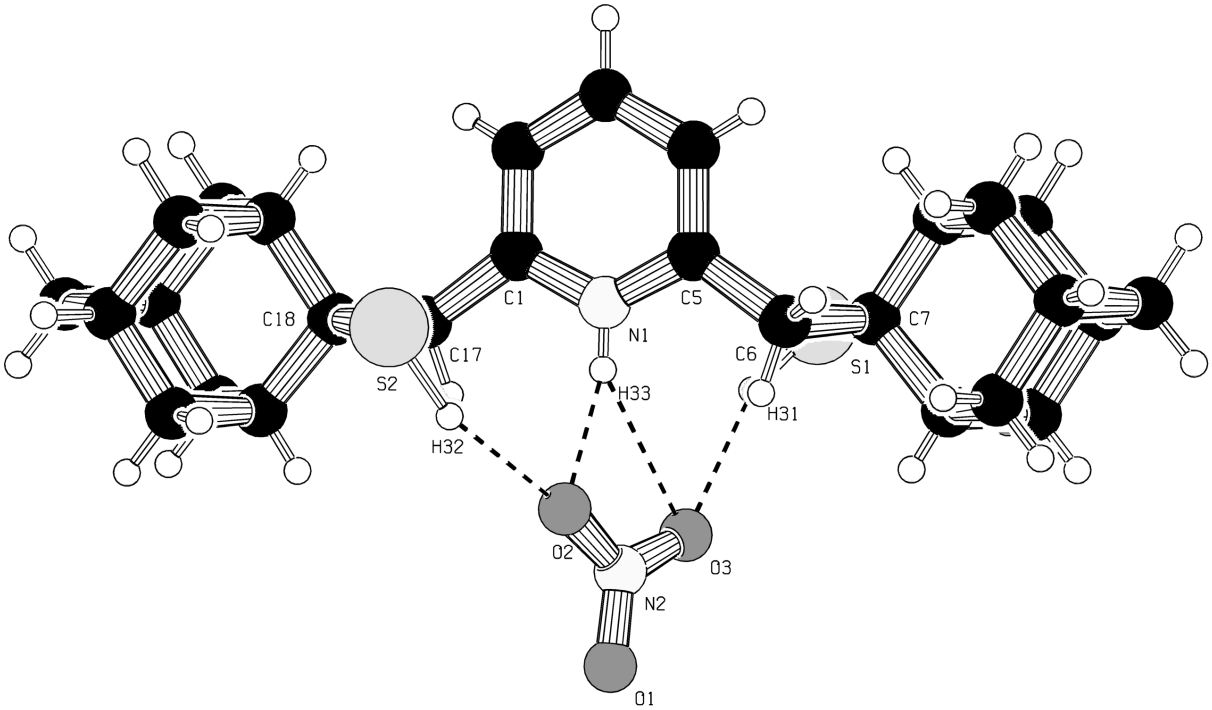
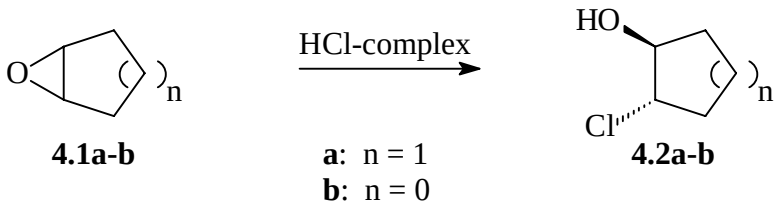


Figure 4.4 *Crystal structure of **3.1b**·HNO_3.*

There is a noteworthy difference between **3.1b**·HCl and **3.1b**·HNO_3. First of all the cavity that is formed for the complexation of HNO_3 is bigger than in the HCl complex. The flexibility of the ligand allows the adjustment of the cavity when larger acids coordinate. The proton H(33) at the pyridine nitrogen forms a strong bond with O(2) (1.92(5) Å) whereas the bond between H(33) and O(3) is longer (2.58(5) Å). Both thiol groups are hydrogen bonded to the oxygens of the acid (H(32)…(O2) 2.26(5) Å and H(31)…O(3) 2.21(5) Å).

4.3 Hydrochlorination of Epoxides Using HCl-complexes.

Addition of HCl to strained heterocyclic rings such as those of epoxides is known from the literature although the reaction is not extensively applied, likely because of the lack of suitable methods to generate mild reaction conditions to perform the ring opening reaction. Addition of hydrogen chloride to a reaction mixture gives an acidic medium which can lead to unwanted side reactions such as epimerization. It is also difficult to control the quantity of hydrogen chloride added. We observed that upon addition of the hydrogen chloride complex **2.1b**·HCl to cyclohexene oxide **4.1a** or cyclopentene oxide **4.1b**, the epoxide is opened though nucleophilic attack of the chloride forming the corresponding epichlorohydrin quantitatively (Scheme 4.1).



4.1a-b **a**: n = 1 **b**: n = 0 **4.2a-b**

Scheme 4.1 *Ring opening of epoxides with hydrogen chloride complexes.*

Although the hydrogen chloride is encapsulated within the molecular structure of the ligand it is apparently not so tightly bond that it cannot react with the epoxide. Ring opening provides the *trans* product selectively within 3 hour as deducted form ^{1}H NMR. No traces of isomerization to the *cis* product is observed. Using the hydrogen chloride complexes mild conditions for ring opening are generated and just one equivalent of hydrogen chloride is added preventing unwanted side reactions. Using 2,6-lutidine·HCl ringopening can also be effectuated, giving a cheap alternative for this reaction.

Ring opening of prochiral cyclohexene oxide and cyclopentene oxide making use of chiral hydrogen chloride complexes like **2.1d**·HCl and **3.11f**·HCl was investigated. When epoxides **4.1a** and **4.1b** were stirred with complexes **2.1d**·HCl and **3.11f**·HCl selective ring opening to the *trans* epichlorohydrins **4.2a** and **4.2b** occurred. Determination of the enantiomeric excess,[6] however, gave only low (0-10%) and unreproducible selectivities. The steric aspects of the ligand seem to have only a minor influence on the approach of the epoxide to the chloride. Thus far no reproducible enantioselective addition has been observed.

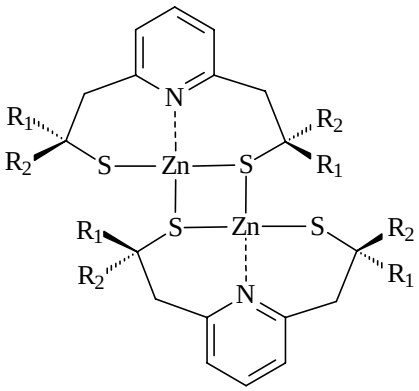
Ring opening of the epoxides with the hydrogen bromide complexes **2.1b**·HBr, **3.1f**·HBr, and **3.11f**·HBr gave rise to the *trans* epibromohydrins **4.3a** and **4.3b**. Again low and unreproducible enantioselectivities with the chiral hydrogen bromide complexes were observed.

4.5 Complexes with Zinc.

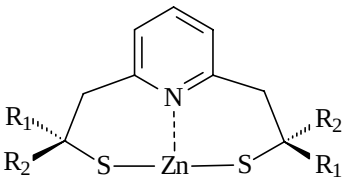
Encapsulation of various metals like Zn[7], Ti,[8] Mo,[9] Os,[10] Zr,[11] and Ru[12] have been reported for **2.1a, 2.1b** and **3.1a**. Molybdenum complexes of both the diol **2.1a** and the dithiol **3.1a** are known as models for molybdenum enzymes.[9] The zinc complexes of pyridine diol **2.1b** and dithiol **3.1a** are of interest as models for the catalytic active zinc at the active site of Horse Liver Alcohol Dehydrogenase (HLADH) although catalytic activity with these complexes is low.[7] In order to examine more closely the complexation abilities of the pyridine alcohols and thiols with zinc various complexes were synthesized.

When pyridine diol **2.1b** was stirred with $Zn(NO_3)_2$ overnight the complex was formed. ^{1}H NMR shows a downfield shift for the pyridine protons indicating that the pyridine ring is involved in the complexation of the zinc. These results are in accordance with the result reported for the complexes of pyridine diols **2.1c** and **2.1d** with $Zn(NO_3)_2$. A chiral zinc complex was obtained by reaction of **2.1e** with $Zn(NO_3)_2$. A relatively large chemical shift for the pyridine protons in the ^{1}H NMR was observed (0.5 ppm for the 3- and 5-hydrogens and 0.6 ppm for the 4-hydrogen). Furthermore the benzylic protons give rise to a AB-system caused by the locked conformation of the complex. The ^{1}H NMR spectrum also indicates an impact on the camphor moiety: the methyl groups are shifted downfield whereas the other alkyl groups are shifted upfield. Complexation of zinc seems to have a great impact on the whole structure of the molecule. When **2.1e** was allowed to form a complex with $Zn(ClO_4)_2$ a similar complex was formed. However, the impact of coordination of this zinc reagent has far less influence on the camphor moiety and only upfield shifts for the alkyl groups are observed. Complexation of $Zn(NO_3)_2$ with the C_s-symmetrical pyridine diol **2.7b** afforded colorless crystals. For this complex also large chemical shifts of the pyridine protons are observed indicating that the complex is formed. Furthermore large downfield shifts for the benzylic proton as well as the methyl group are observed. The signals for the adamantyl moiety becomes extremely complicated on complexation.

Zinc complexes with pyridine dithiols **3.1** have been reported previously.[7] Zinc complexes of **3.1a** and **3.1c** were found to give dimeric complexes **4.4**, whereas, the zinc complex of **3.1d** owing to the large fluorenyl groups gave monomeric zinc complex **4.5**. We have assumed that for these complexes to act as a model for the enzyme HLADH they must be monomeric otherwise the zinc atom is coordinatively saturated and unable to act as a catalyst.



4.4a-c



4.5d,f

a: R_1,R_2 = phenyl
b: R_1,R_2 = adamantyl
c: R_1,R_2 = methyl
d: R_1,R_2 = fluorenyl
f: R_1,R_2 = fenchyl

Since the allylic moieties of pyridine dithiols **3.1b** and **3.1f** are bulky complexation of zinc could afford monomeric complexes. When dithiol **3.1b** was stirred with $Zn(NO_3)_2$ a poorly soluble dimeric zinc complex **4.4b** precipitated as a white solid as was observed in the ^{1}H NMR. Since all benzylic protons are nonequivalent these protons give rise to a set of eight signals. Apparently the adamantyl moiety does not shield the zinc enough to prevent dimerization. When pyridine dithiol **3.1b** was allowed to complex with $ZnCl_2$ in methanol again the dimeric zinc complex **4.4b** precipitated. Removal of the solvent afforded a second product. The ^{1}H NMR of this product shows extremely large downfield shifts of the pyridine protons (1.19 ppm for the 4-hydrogen and 0.54 ppm for the 3- and 5-hydrogens). Furthermore methanol is still present in the product. Evaporation of methanol under high vacuum afforded a solid that was insoluble in chloroform. Addition of ethanol led to dissolution of the solid indicating that alcohol is embedded in the complex. Although the chemical shifts of 1.19 ppm for the 4-hydrogen and 0.54 ppm for the 3- and 5-hydrogen are very large for a zinc complex qualitative analysis revealed the presence of zinc. Crystals Suitable for X-ray diffraction were grown from chloroform/hexane (Figure 4.5).

X-ray crystallographic structure determination reveals the structure to be dimeric complex **4.6** in which HCl is encapsulated, although in an unusual manner, in the cavity of the pyridine dithiol. The Cl from the HCl is strongly coordinated to an equivalent of $ZnCl_2$ (Cl(2)…Zn 2.2425(8) Å). The fourth coordination place of this $ZnCl_2$ is filled with a methanol or ethanol molecule. The initial reaction took place in methanol, after removal of a part of the methanol and upon addition of ethanol the fourth coordination position is filled with methanol as well as ethanol in a ratio of 56:44. The hydroxyl groups of the alcohols are hydrogen bonded to the chloride atom of the other part of the dimer (2.32(3) Å). These two hydrogen bonds keep the entire structure together. Remarkable in this complex is the binding of the hydrogen chloride by the thiol groups in a *trans* fashion. In the complex of **3.1b**·HCl the HCl is bonded in a *cis* fashion. The coordination is likely due to influences of the zinc chloride on the crystal packing.
The mechanism of formation of this complex is probably as follows. Initially addition of $ZnCl_2$ to the free ligand **3.1b** led to the formation of the monomeric zinc complex upon which two

equivalents of HCl are released. This monomeric complex is unstable and associates to the dimer **4.4b**. The released HCl is encapsulated by free ligand and this complex forms a stable bond with $ZnCl_2$ still present in the mixture. After 1/3 of the ligand has formed the dimeric zinc **4.4b** complex the remaining 2/3 of the ligands is converted to the HCl complex.

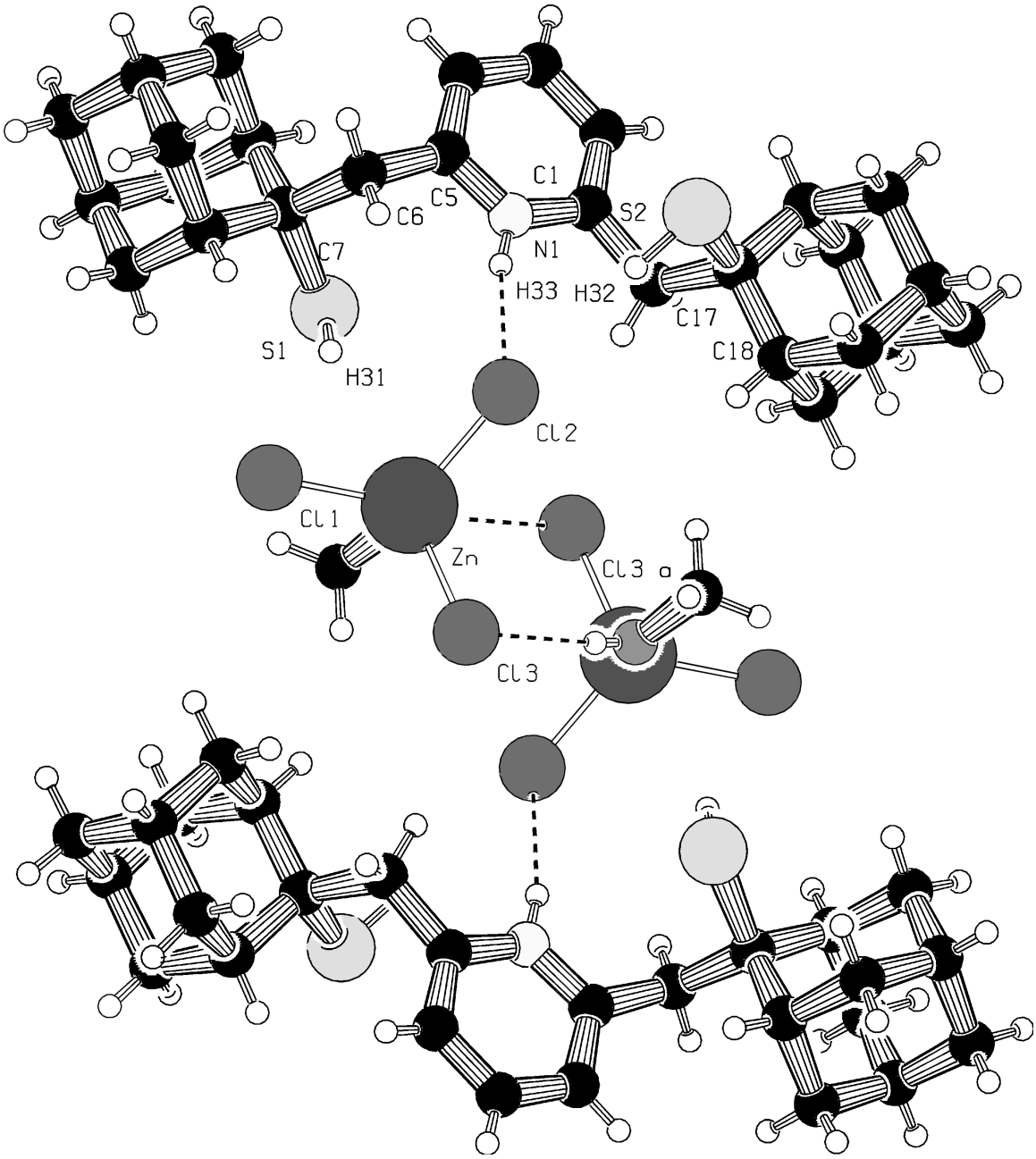


Figure 4.5 *Crystal structure of **4.6.***

When chiral pyridine dithiol **3.1f** was added to a solution of $Zn(NO_3)_2$ in methanol and stirred for 3 h and after careful removal of the solvent a white solid was obtained. ^{1}H NMR in $CDCl_3$ revealed the monomeric zinc complex **4.5f**. The benzylic protons give rise to only four signals whereas for a dimeric structure eight signals are expected. Mass spectroscopy (electron spray and exact mass) on this complex establishes a monomeric complex. The complex of **3.1f**

with $Co(NO_3)_2$ surprisingly showed a dimeric complex as indicated by ^1H NMR. The monomeric Co complex probably is less stable than the monomeric zinc complex and dimerizes.

4.6 Conclusions.

Complexations of HCl with pyridine diol **2.1e** and with the pyridine thiols **3.11f** and **3.1b** were found to be successful. The complex **3.1b**·HCl showed a remarkable physical property, which point towards complexation of covalent HCl. ^1H NMR data, X-ray diffraction, and infrared spectroscopy of the DCl complex, however, point towards an ionic character of the HCl bond. X-ray diffraction of the C_s-symmetrical pyridine diol **2.7b** complex with HCl revealed that only one of the hydroxyl groups coordinates with the chloride. Complexes with the pyridine diol **2.1b** and thiols **3.1f** and **3.11f** were formed with HBr. Addition of cyclohexene oxide and cyclopentene oxide to these HBr and HCl complexes gave the bromo- and chlorohydrins. When chiral complexes were used low and nonreproducible enantiomeric excesses were obtained. The complexes probably do not shield the acids enough so that enantioselection can occur. Complexes with HNO_3 can also be formed even with the oxidizable dithiol **3.1b** as shown by X-ray analysis. Pyridine diols **2.1b**, **2.1e** and **2.7b** easily give complexes with Zn^{2+}. Complexation of $Zn(NO_3)_2$ with pyridine dithiol **3.1b** gave a dimeric complex **4.4b** whereas complexation with **3.1f** afforded a monomeric complex **4.5f**. When $ZnCl_2$ was used for complexation with **3.1b** some dimeric zinc complex **4.4b** was formed; release of HCl in this reaction gave rise to complexation of the HCl by the ligand and formation of the dimeric HCl·$ZnCl_2$ complex **4.6**. The pyridine diols and dithiols are perfectly capable of complexating metals as well as small acids like HCl, HBr and HNO_3. The size of the cavity in which these substrates bind is flexible and adapts to such a size that the metal or acid perfectly fits the cavity.

4.7 Experimental Section.

General Remarks: See Chapter 2. HCl was prepared from NaCl and H_2SO_4. HBr and DCl were used from lecture bottles. DCl was dried over D_2SO_4.

3.1b·HCl

A solution of dithiol **3.1b** (0.10 g, 0.23 mmol) in 5 mL of $CHCl_3$ under an argon atmosphere was cooled to 0 °C. At this temperature a freshly prepared solution of HCl in chloroform was added. The mixture was stirred for 30 min and after careful evaporation of the solvent at reduced pressure the crude HCl complex was isolated as a white powder, which was crystallized from methanol to afford **3.1b**·HCl as colorless needles (0.11 g., 0.22 mmol, 98%). mp 229-230 °C; ^1H NMR ($CDCl_3$): δ 1.58-1.94 (m, 20H), 2.25 (m, 4H), 2.52 (m, 4H), 3.22 (s, 2H), 4.04 (s, 4H), 7.44 (d, *J* = 8.05 Hz, 2H), 8.11 (dd, *J* = 8.05 Hz, 1H); ^{13}C NMR

($CDC1_3$): δ 27.04 (CH), 27.43 (CH), 33.21 (CH_2), 33.63 (CH_2), 37.77 (CH), 38.99 (CH_2), 42.44(CH_2), 56.16 (C), 124.78 (CH), 142.54 (CH), 155.10 (C); HRMS calcd for $C_{27}H_{38}NS_2$ Cl 475.698, found 439.237 (-HCl)

3.1b.DCl

This product was synthesized according to the HCl analogue **3.1b**·HCl, starting from the dithiol compound **3.1b** (0.13 g, 0.30 mmol) in 5 mL of $CDCl_3$ to which a freshly prepared solution of DCl in $CDCl_3$ was added. Careful evaporation of the solvent yielded the DCl complex as a white powder (0.13 g., 0.28 mmol, 95%). mp 228-230 °C; ^{1}H NMR ($CDCl_3$): δ 1.58-1.94 (m, 20H), 2.25 (m, 4H), 2.52 (m, 4H), 3.22 (s, 2H), 4.04 (s, 4H), 7.44 (d, *J* = 8.05 Hz, 2H), 8.11 (dd, *J* = 8.05 Hz, 1H); ^{13}C NMR ($CDC1_3$): δ 27.0 (CH), 27.4 (CH), 33.2 (CH_2), 33.6 (CH_2), 37.7 (CH), 38.9 (CH_2), 42.5(CH_2), 56.2 (C), 124.7 (CH), 142.5 (CH), 155.1 (C); IR: 3425 (br), 2910 (s), 2860 (s), 2665 (br), 2570 (br), 2480 (br), 2211 (s), 2005 (br), 1630 (s), 1615 (s), 1450 (s), 1100 (s), 920 (s), 735 (s), 720 (s) cm^{-1}.

Crystal Structure of 3.1b·HCl.

Crystal Data: Formula: $[C_{27}H_{38}NS_2]^+.Cl^-.(CH_2Cl_2)$, M = 561.12. Suitable transparent block-shaped crystals of approximate dimensions of 0.17 x 0.41 x 0.05 mm were obtained by recrystallization from dichloromethane. Orthorhombic, P*bcn*, *a* = 15.491(1), *b* = 12.989(1), *c* = 28.081(2) Å, V = 5650.3(7) Å , Z = 8, D = 1.319 g cm , λ(MoK$\bar{\alpha}$) = 0.71073 Å, μ = 4.91 cm, F(000) = 2834, T = 130 K. *Data collection:* The data were collected on an Enraf-Nonius *CAD-4F*^{2} diffractometer (Mo tube, 50 kV, 40 mA, monochromated Mo-K$\bar{\alpha}$ radiation, Δω = 1.05 + 0.34 tg θ), range 8.35° < θ < 18.4°, reflections collected: 7388 independent reflections: 5529. *Solutions and refinement*: The structure was solved by Patterson methods and extension of the model was accomplished by direct methods applied to difference structure factors using the program *DIRDIF*.[13] wR(F^2) = 0.112 for 5529 reflections with $F_o^2 \geq 0$ and R(*F*) = 0.044 for 4507 unique observed reflections with $F_o \geq 4.0\ \sigma(F_o)$ and 477 parameters.

Table 4.1: *Interatomic distances and selected bond angles for compound **3.1b**·HCl*

Interatomic Distances (Å)					
S(1)[a]	-C(7)	1.850(2)[b]	C(17)	-C(18)	1.555(3)
S(2)	-C(18)	1.850(2)	H(31)	-S(1)	1.25(3)
N(1)	-C(1)	1.339(3)	H(32)	-S(2)	1.22(5)
N(1)	-C(5)	1.346(3)	H(33)	-N(1)	0.86(3)
C(1)	-C(6)	1.504(3)	H(31)	-Cl(1)	2.58(3)
C(5)	-C(17)	1.501(3)	H(32)	-Cl(1)	2.45(5)
C(6)	-C(7)	1.554(3)	H(33)	-Cl(1)	2.19(3)

Bond angles (deg.)							
C(1)	-N(1)	-C(5)	124.7(2)	Cl(1)	-H(31)	-S(1)	162(3)
C(1)	-C(6)	-C(7)	116.9(2)	Cl(1)	-H(32)	-S(2)	168(3)
C(5)	-C(17)	-C(18)	116.7(2)	Cl(1)	-H(33)	-N(1)	178(3)
S(2)	-C(18)	-C(17)	107.01(16)	H(31)	-S(1)	-C(7)	97.8(17)
S(1)	-C(7)	-C(6)	107.78(16)	H(32)	-S(2)	-C(18)	97.8(19)
N(1)	-C(1)	-C(6)	118.1(2)	H(33)	-N(1)	-C(1)	118.5(19)
N(1)	-C(5)	-C(17)	118.2(2)	H(33)	-N(1)	-C(5)	116.9(19)

[a] The numbering for the crystal data does not follow the numbering used in nomenclature.

[b] Standard deviation in parentheses.

2.1e·HCl

To a solution of the free ligand **2.1e** (0.20 g, 0.49 mmol) 20 mL in dichloromethane was passed through a slow stream of HCl for 5 min. The mixture was stirred for 1 h and the solvent was evaporated. The solid was recrystallized from water/ethanol (1:2) yielding a colorless solid (0.21g, 0.47 mmol, 95.6 %): mp >200°C; $[\alpha]^{23}_{D}$ +189° (*c* 0.4, chloroform); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (s,6H), 1.01 (s, 6H), 1.07 (s, 6H), 1.36 (m, 4H), 1.56 (m, 6H), 1.72 (m, 4H), 2.89 (d, *J* = 12.81 Hz, 2H), 3.69 (d, *J* = 12.81 Hz, 2H), 4.18 (s, 2OH), 7.43 (d, *J* = 8.06 Hz, 2H), 8.04 (t, *J* = 8.06 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 9.58 (q), 20.99 (q), 21.14 (q), 27.13 (t), 30.57 (t), 42.40 (t), 43.88 (t), 44.93 (d), 48.96 (s), 53.37 (s), 80.88 (s), 125.12 (d), 143.7 (d), 155.38 (s). HRMS calcd 447.290; no proper HRMS could be obtained; CI(NH_3) gave a molecular ion at m/e 412 (-HCl). Anal. Calcd for $C_{27}H_{42}NO_2Cl$: C, 72.37; H, 9.45; N, 3.13, Cl 7.91. Found C, 72.21; H, 9.20; N, 3.20, Cl 7.97.

Crystal Structure of 2.1e·HCl

Crystal Data: Formula: $C_{27}H_{42}NO_2^+Cl^-$, M = 448.09, Suitable crystals for an X-ray crystallographic determination were grown from a solution of **2.1e**·HCl in ethanol/water upon slow evaporation of the ethanol. The colorless plate-shaped crystal, used for characterization and data collection, was of approximate size 0.09 x 0.45 x 0.50 mm. Monoclinic, $P2_1$, *a* = 14.915(1), *b* = 11.853(1), *c* = 7.137(1) Å, β= 93.153(8)°, *V* = 1259.8(2) Å, *Z* = 2, D_x = 1.181 g cm^{-1}, λ(MoK$\bar{\alpha}$) = 0.71073 Å, μ = 1.75 cm , *F*(000) = 488. *Data collection*: The data were collected on an Enraf-Nonius *CAD-4F* diffractometer (Mo tube, 50 kV, 40 mA, monochromated Mo-Kα radiation, Δω = 1.05 + 0.34 tg θ); T = 130 K, range 16.24° < θ < 20.15°, reflections collected: 2541 independent reflections 2371. *Solutions and refinement*: The structure was solved by Patterson methods and extension of the model was accomplished by direct methods applied to difference structure factors using the program *DIRDIF*. Refined anisotropically by full-matrix least squares based on F^2 (SHELXL); data/parameters

2371/448 ; $R(F)$ = 0.0331 [$F_o \geq 4.0\ \sigma(F_o)$], $wR(F^2)$ = 0.0788 [$F^2>0$]; absolute-structure parameters; maximal residual electron density (±0.26(5) e/Å^3). The program PLATON has been used for graphical representations of the crystal structure.

Table 4.2: *Interatomic distances and selected bond angles for compound **2.1e**·HCl*

Interatomic Distances (Å)					
O(1)[a]	-C(7)	1.434(3)[b]	C(17)	-C(18)	1.550(3)
O(2)	-C(18)	1.431(3)	H(31)	-O(1)	0.79(4)
N(1)	-C(1)	1.349(3)	H(32)	-O(2)	0.97(5)
N(1)	-C(5)	1.344(3)	H(33)	-N(1)	0.85(4)
C(1)	-C(17)	1.495(4)	H(31)	-Cl(1)	2.48(4)
C(5)	-C(6)	1.501(3)	H(32)	-Cl(1)	2.33(5)
C(6)	-C(7)	1.554(3)	H(33)	-Cl(1)	2.23(4)

Bond angles (deg.)							
C(1)	-N(1)	-C(5)	124.8(2)	Cl(1)	-H(31)	-O(1)	147(4)
N(1)	-C(1)	-C(17)	117.8(2)	Cl(1)	-H(32)	-O(2)	162(4)
N(1)	-C(5)	-C(6)	118.4(2)	Cl(1)	-H(33)	-N(1)	177(4)
C(5)	-C(6)	-C(7)	116.54(18)	H(31)	-O(1)	-C(7)	109(4)
O(1)	-C(7)	-C(6)	107.32(19)	H(32)	-O(2)	-C(18)	110(3)
C(1)	-C(17)	-C(18)	113.3(3)	H(33)	-N(1)	-C(1)	117(3)
O(2)	-C(18)	-C(17)	107.11(18)	H(33)	-N(1)	-C(5)	118(3)

[a] The numbering for the crystal data does not follow the numbering used in nomenclature.

[b] Standard deviation in parentheses.

2.7b·HCl

This material was prepared in according to the procedure for **2.1e**·HCl starting from **2.7b** (0.55 g, 1.35 mmol). A colorless solid crystallized after addition of hexane (0.53 g, 1.20 mmol, 89%): mp 193-194°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 2H), 1.24 (m, 2H), 1.4-1.8 (m, 12H), 1.878 (s, 6H), 2.43 (m, 6H), 3.19 (s, 3H), 4.22 (s, 1H), 6.08 (br, 2OH), 7.51 (m, 2H), 8.08 (t, J = 7.81 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 26.21 (q), 26.74 (d), 32.68 (t), 32.73 (t), 33.96 (t), 34.87 (t), 36.45 (d), 36.57 (d), 37.66 (t), 50.48 (d), 79.45 (s), 125.30 (d), 127.48 (d), 142.76 (d), 154.74 (s), 156.58 (s). HRMS calcd 443.259; no proper HRMS could be obtained; CI(NH_3) gave a molecular ion at m/e 408 (-HCl). Anal. Calcd for $C_{55}H_{78}N_2O_4Cl_4$: C, 67.89; H, 8.08; N, 2.88; Cl 14.57. Found C, 67.21; H, 8.05; N, 2.86; Cl, 14.43.

Crystal Structure 2.7b·HCl

Crystal Data: Formula: $([C_{27}H_{38}NO_2]^+.Cl^-)_2.CH_2Cl_2$, M = 973.05, Suitable colorless crystals were obtained by recrystallization from CH_2Cl_2. The crystal, used for characterization and data collection, was a parallelepiped of approximate size 0.40 x 0.44 x 0.46 mm. The asymmetric units consists of five moieties: two anion complexes, two chlorides anions and one molecule dichloromethane solvent molecule. Monoclinic $P2_1/a$, a = 13.656(4), b = 10.300(1), c = 35.476(5) Å, β = 95.43(2)°, V = 4967.5(17) Å^3, Z = 4, D_x = 1.301 gcm^{-3}, λ(MoK$\bar{\alpha}$) = 0.71073 Å, μ = 2.9 cm^{-1}, F(000) = 2088, T = 130 K. *Data collection*: The data were collected on an Enraf-Nonius *CAD*-4F^2 diffractometer (Mo tube, 50 kV, 40 mA, monochromated Mo-K$\bar{\alpha}$ radiation, Δω = 0.80 + 0.34 tg θ); range 18.16° < θ < 20.52°. Reflections collected: 10746 independent reflections 9688. *Solutions and refinement:* The structure was solved by Patterson methods and extension of the model was accomplished by direct methods applied to difference structure factors using the program *DIRDIF*. Final refinement on F^2 carried out by full-matrix least-squares techniques converged at $wR(F^2)$ = 0.1402 for 9688 reflections with $F_o^2 \geq 0$ and $R(F)$ = 0.0424 for 7896 reflections with $F_o \geq 4.0$ $\sigma(F_o)$ and 898 parameters.

Table 4.3 : *Interatomic distances and selected bond angles for unit 1 of compound **2.7b**·HCl*

Interatomic Distances (Å) of unit 1					
O(1)[a]	-C(8)	1.431(3)[b]	H(102)	-Cl(3)	2.18(3)
O(2)	-C(26)	1.431(3)	H(101)	-O(2)	2.03(4)
O(1)	-H(101)	0.77(4)	H(111)	-N(1)	0.87(3)
O(1)	-H(111)	2.51(3)	C(6)	-C(7)	1.511(3)
O(2)	-H(102)	0.88(3)	C(7)	-C(8)	1.589(3)
Cl(3)	-H(111)	2.36(3)	C(7)	-C(26)	1.590(3)
N(1)	-C(6)	1.356(3)			

Bond angles (deg.) of unit 1							
N(1)	-C(6)	-C(7)	120.87(18)	H(111)	-N(1)	-C(6)	116(2)
C(6)	-C(7)	-C(8)	108.31(17)	C(8)	-O(1)	-H(101)	105(3)
C(6)	-C(7)	-C(26)	115.65(17)	C(26)	-O(2)	-H(102)	109.4(18)
O(1)	-C(8)	-C(7)	108.35(17)	O(2)	-H(102)	-Cl(3)	160(3)
O(2)	-C(26)	-C(7)	109.08(16)	O(1)	-H(101)	-O(2)	141(4)
Cl(3)	-H(111)	-N(1)	158(3)				

[a] The numbering for the crystal data does not follow the numbering used in nomenclature.

[b] Standard deviation in parentheses.

Table 4.4 : *Interatomic distances and selected bond angles for unit 2 of compound **2.7b**·HCl.*

Interatomic Distances (Å) of unit 2					
O(3)[a]	-C(35)	1.439(3)[b]	C(34)	-C(45)	1.589(3)
O(4)	-C(45)	1.436(3)	N(2)	-C(33)	1.355(3)
O(3)	-H(103)	0.81(3)	Cl(4)	-H(112)	2.38(3)
O(4)	-H(104)	0.84(4)	H(112)	-N(2)	0.85(3)
O(3)	-H(104)	1.94(4)	H(112)	-O(4)	2.47(3)
C(33)	-C(34)	1.514(3)	H(103)	-Cl(4)	2.27(3)
C(34)	-C(35)	1.585(3)			

Bond angles (deg.) of unit 2							
N(2)	-C(33)	-C(34)	120.16(19)	C(35)	-O(3)	-H(103)	108(2)
O(3)	-C(35)	-C(34)	108.82(16)	C(35)	-O(3)	-H(104)	106.6(12)
O(4)	-C(45)	-C(34)	108.72(17)	C(45)	-O(4)	-H(104)	106(3)
O(3)	-H(103)	-Cl(4)	166(3)	C(33)	-C(34)	-C(35)	115.71(17)
O(3)	-H(104)	-O(4)	141(4)	C(33)	-C(34)	-C(45)	106.84(17)
Cl(4)	-H(112)	-N(2)	149(3)	N(2)	-H(112)	-O(4)	104(2)
H(112)	-N(2)	-C(33)	120(2)				

[a] The numbering for the crystal data does not follow the numbering used in nomenclature.

[b] Standard deviation in parentheses.

2.1b·HBr

The adamantanone adduct **2.1b** (0.25 g, 0.61 mmol) was dissolved in 10 mL of chloroform and HBr was slowly passed through the solution for 5 min at 0°C. After removal of the solvent the product was recrystallized twice from ethanol yielding a colorless solid (44%, 0.13 g, 0.27 mmol): mp > 240°C; IR (KBr): 3370, 2905, 1635, 1625, 1070, 1025, 925, 820, 760; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.4-2.1 (m, 24H), 2.26 (d, *J* = 12.94 Hz, 4H), 3.67 (s, 4H), 3.84 (s, 2H), 7.37 (d, *J* = 7.81 Hz, 2H), 8.09 (t, *J* = 7.81 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 27.16 (d), 27.37 (d), 32.72 (t), 34.44 (t), 37.07 (d), 38.24 (t), 40.65 (t), 75.59 (s), 125.05 (d), 142.72 (d), 154.45 (s); HRMS calcd 487.209; found 407.282 (-HBr). Anal. Calcd for $C_{27}H_{38}NO_2Br$: C, 66.39; H, 7.84; N, 2.87, Br 16.36. Found C, 66.27; H, 7.80; N, 2.87, Br 16.36.

3.11f·HBr

This product was prepared according to the method described for **2.1b**·HCl starting from **3.11f** (0.75 g, 2.7 mmol). After HBr addition was stopped hexane was added and the complexes precipitated from the solution. the product was recrystallized from chloroform/hexane affording colorless needles (0.92 g, 2.6 mmol, 95%). mp 217-218 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.05 (s, 3H), 1.14 (s, 3H), 1.18 (m, 1H), 1.34 (d, *J* = 11.7 Hz, 1H), 1.40 (m, 1H),

1.56 (s, SH), 1.61 (m, 1H), 1.66 (m, 1H), 2.27 (d, *J* = 11.0 Hz, 1H), 2.38 (m, 1H), 2.99 (s, 3H), 3.26 (d, *J* = 17.2 Hz, 1H), 4.47 (d, *J* = 17.2 Hz, 1H), 7.44 (d, *J* = 7.69 Hz, 1H), 8.11 (dd, *J* = 8.05 Hz, *J* = 7.69 Hz, 1H), 8.79 (d, *J* = 8.05 Hz, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 17.68 (q), 19.16 (q), 24.41 (t), 26.04 (q), 29.42 (q), 33.77 (t), 40.23 (t), 44.28 (t), 45.37 (s), 50.70 (d), 56.21 (s), 63.29 (s), 124.69 (d), 125.17 (d), 143.43 (d), 153.54 (s), 157.82 (s); HRMS calcd. 355.097, found 275.171 (-HBr). Anal. Calcd. for $C_{17}H_{26}NSBr$: C, 57.30; H, 7.35; N, 3.93; S, 9.00. Found C, 57.36; H, 7.37; N, 3.94, S; 8.98.

3.1b·HBr

This product was prepared analogously to **2.1b**·HBr starting from a solution of dithiol **3.1b** 0.10 g, 0.23 mmol) in 10 mL of $CHCl_3$ at 0°C. Evaporation of the solvent at reduced pressure yielded the crude HBr complex as a white powder, which was crystallized from $CHCl_3$/hexane to afford **3.1b**·HBr as colorless needles (0.09 g, 0.17 mmol, 75%): mp > 220 °C; ^{1}H NMR ($CDCl_3$): δ 1.8 (m, 20H), 2.27 (d, J=12.9 Hz, 4H), 2.52 (d, J=11.7 Hz), 4H), 3.27 (s, SH), 4.09 (s, 4H), 7.45 (d, *J* = 8.1 Hz, 2H), 8.15 (dd, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDC1_3$): δ 27.79 (CH), 28.21 (CH), 33.99 (CH_2), 34.38 (CH_2), 38.54 (CH), 39.78 (CH_2), 42.84 (CH_2), 57.08 (C), 99.88 (C), 125.77 (CH), 143.64 (CH), 155.94 (C); HRMS calcd for $C_{27}H_{38}NS_2$ Br 519.163, found 439.237 (-HBr).

2.1b·HNO3

The diol adduct **2.1b** (0.20 g, 0.49 mmol) was dissolved in 10 mL of chloroform and cooled to 0°C. HNO_3 100% (32 mg, 0.5 mmol) was added and stirring was continued for 30 min. After removal of the solvent the product was recrystallized from methanol yielding a white solid (95%, 0.22 g, 0.47 mmol): mp 194-196°C; IR (KBr): 3385, 2905, 1635, 1450, 1321, 1200, 1070, 1025, 930, 825, 760; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 (d, *J* = 13.19 Hz, 4H), 1.71 (s, 8H), 1.87 (m, 12H), 2.13 (d, *J* = 10.5 Hz, 4H), 3.42 (s, 4H), 7.42 (d, *J* = 7.82 Hz, 2H), 8.12 (t, *J* = 7.82 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 26.93 (d), 27.17 (d), 32.56 (t), 34.34 (t), 36.77 (d), 38.03 (t), 41.83 (t), 75.37 (s), 125.01 (d), 143.01 (d), 154.48 (s). HRMS calcd. 470.278; found 407.282 (-HNO_3). Anal. Calcd for $C_{27}H_{38}N_2O_5$: C, 68.91; H, 8.14; N, 5.95. Found C, 68.64; H, 8.11; N, 6.01.

3.1b·HNO_3

This product was prepared according to the method used for the preparation of **2.1d**·HNO_3, at 0°C starting from dithiol **3.1b** (0.45 g, 1.03 mmol). The product was recrystallized from $CHCl_3$/hexane by slow evaporation of the solvent (mainly chloroform) to obtain **3.1b**·HNO_3 as colorless crystals (0.34 g., 0.69 mmol, 67%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.8-2.2 (m, 20H), 2.40 (d, *J* = 11.7 Hz, 2H), 2.65 (d, *J* = 11.7 Hz, 2H), 3.94 (s, 4H), 7.65 (d, *J* = 7.7 Hz, 2H), 8.24 (t, *J* = 7.7 Hz, 1H).

Crystal Structure of HNO_3 complex of 3.1b

Crystal Data: *Formula*: $[C_{27}H_{38}NS_2]^+.[NO_3]^-$, M = 502.74, Suitable colorless thin plate-shaped crystals of approximate size 0.02 x 0.23 x 0.32 mm were obtained by recrystallization from chloroform/hexane. monoclinic, *Pc*, *a* = 6.824(2), *b* = 16.118(4), *c* = 11.972(4) Å, , β = 102.68(3)°, *V* = 1284.7(7) Å, *Z* = 2, D_x = 1.300 g cm^{-1}, λ(MoK$\bar{\alpha}$) = 0.71073 Å, μ = 2.4 cm , *F*(000) = 540; T = 130 K. The asymmetric unit consists of two moieties: a cation complex and as counter anion NO_3^-. *Data collection:* The data were collected on an Enraf-Nonius *CAD-4F*^{2} diffractometer (Mo tube, 50 kV, 40 mA, monochromated Mo-K$\bar{\alpha}$ radiation, Δω = 1.05 + 0.34 tg θ), range 8.35° < θ < 18.41°, reflections collected: 5373 independent reflections: 2542. *Solutions and refinement*: The structure was solved by Patterson methods and extension of the model was accomplished by direct methods applied to difference structure factors using the program *DIRDIF*. Final refinement converged at *wR*(F^2) = 0.0883 for 2542 reflections with $F_o^2 \geq 0$ and 342 parameters and *R*(*F*) = 0.0457 for 1862 reflections with $F_o \geq 4.0\ \sigma(F_o)$.

Table 4.5*: Interatomic distances and selected bond angles for compound* ***3.1b·****HNO_3.*

Interatomic Distances (Å)					
S(1)[a]	-C(7)	1.838(5)[b]	S(2)	-H(32)	1.43(6)
S(2)	-C(18)	1.861(6)	S(1)	-H(31)	1.24(5)
N(1)	-C(1)	1.344(7)	O(1)	-N(2)	1.241(6)
N(1)	-C(5)	1.341(7)	O(2)	-N(2)	1.259(6)
N(1)	-H(33)	0.87(5)	O(3)	-N(2)	1.244(7)
C(1)	-C(17)	1.508(7)	H(33)	-O(2)	1.92(5)
C(5)	-C(6)	1.502(7)	H(33)	-O(3)	2.58(5)
C(6)	-C(7)	1.550(7)	H(32)	-O(2)	2.26(5)
C(17)	-C(18)	1.558(7)	H(31)	-O(3)	2.21(5)

Bond angles (deg.)							
C(1)	-N(1)	-C(5)	124.8(5)	O(1)	-N(2)	-O(3)	121.2(4)
N(1)	-C(1)	-C(17)	116.8(5)	O(1)	-N(2)	-O(2)	120.6(4)
N(1)	-C(5)	-C(6)	117.2(5)	O(2)	-N(2)	-O(3)	118.2(4)
C(5)	-C(6)	-C(7)	115.3(4)	O(2)	-H(33)	-N(1)	162(5)
S(1)	-C(7)	-C(6)	108.3(3)	O(3)	-H(33)	-N(1)	143(4)
C(1)	-C(17)	-C(18)	115.8(5)	C(18)	-S(2)	-H(32)	92(2)
S(2)	-C(18)	-C(17)	107.9(3)	C(7)	-S(1)	-H(31)	92(2)
C(1)	-N(1)	-H(33)	117(3)	S(2)	-H(32)	-O(2)	156(3)
C(5)	-N(1)	-H(33)	118(3)	S(1)	-H(31)	-O(3)	160(3)

[a] The numbering for the crystal data does not follow the numbering used in nomenclature.

[b] Standard deviation in parentheses.

General procedure for ring opening of cyclohexene oxides 4.1a and 4.1b.

To a stirred solution of epoxide **4.1** (0.25 mmol) in 5 mL of CH_2Cl_2 was added the hydrogen chloride or hydrogen bromide complex (0.25 mmol) stirring continued for 3h in which the reaction ran to completion. The solution was filtered and the e.e. and conversion were measured by means of chiral GC (Chiradex BTA (astec) 50m x 0.25 mm x 0.25 μm).

trans-2-chlorocyclohexanol 4.2a

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.31 (m, 3H), 1.72 (m, 3H), 2.10 (m, 2H), 2.59 (s, OH), 3.48 (m, 1H), 3.73 (m, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 23.66 (t), 25.32 (t), 32.87 (t), 34.87 (t), 67.16 (d), 77.53 (d).

trans-2-chlorocyclopentanol 4.2b

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.59 (m, 1H), 1.84 (m, 3H), 2.10 (s, OH), 2.14 (m, 2H), 2.25 (m, 1H), 4.00 (m, 1H), 4.24 (m, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 20.10 (t), 30.87 (t), 32.85 (t), 65.33 (d), 79.91 (d).

trans-2-bromocyclohexanol 4.3a

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30 (m, 3H), 1.67 (m, 1H), 1.79 (m, 2H), 2.11 (m, 1H), 2.30 (m, 1H), 2.46 (s, OH), 3.58 (m, 1H), 3.87 (m, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 24.03 (t), 26.59 (t), 33.43 (t), 36.12 (t), 61.76 (d), 77.38 (d).

trans-2-bromocyclopentanol 4.3b

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.55 (m, 1H), 1.78 (m, 2H), 1.96 (m, 1H), 2.13 (m, 1H), 2.31 (m, 1H), 2.93 (s, OH), 4.00 (m, 1H), 4.29 (m, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 19.84 (t), 30.92 (t), 33.63 (t), 56.82 (d), 80.18 (d).

Complexation of $Zn(NO_3)_2$ with 2.1b

To a stirred solution of **2.1b** (0.10 g, 0.25 mmol) in chloroform (2 mL) was added a solution of $Zn(NO_3)_2.6H_2O$ (74 mg, 0.25 mmol) in methanol (1 mL). The mixture was stirred overnight and concentrated. The solid was washed with dichloromethane and recrystallized from ethyl acetate/methanol by evaporation of the methanol (0.11 g, 0.19 mmol, 78%): ^{1}H NMR (300 MHz, CD_3OD): δ 1.38 (m, 4H), 1.50 (s, 4H), 1.62 (m, 10H), 1.76 (s, 2H), 2.11 (m, 4H), 2.27 (m, 4H), 3.14 (s, 4H), 7.07 (d, *J* = 7.69 Hz, 2H), 7.50 (t, *J* = 7.69 Hz, 1H); Anal. Calcd for $C_{27}H_{37}N_3O_8Zn$: C, 54.32; H, 6.25; N, 7.04. Found C, 54.31; H, 6.27; N, 7.04.

Complexation of $Zn(NO_3)_2$ with 2.1d

This material was prepared according to the procedure reported above for the complexation of **2.1b** starting from **2.1d** (70 mg, 0.17 mmol) and $Zn(NO_3)_2.6H_2O$ (50 mg, 0.17 mmol) After stirring overnight in a mixture of chloroform/methanol (1:1) the solvent was removed and the solid was washed with hexane. After recrystallization form chloroform/hexane the product was obtained as colorless crystals in which methanol is embedded (93 mg, 0.15 mmol, 91%): mp 168-170°C; $[\alpha]^{23}_D$ –5.0 (*c* 0.6, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (s,6H), 0.92 (s, 6H), 1.00 (s, 6H), 1.08 (m, 2H), 1.43 (m, 6H), 1.74 (m, 6H), 2.99 (d, *J* = 13.18 Hz, 2H), 3.30 (d, *J* = 13.18 Hz, 2H), 7.52 (d, *J* = 8.06 Hz, 2H), 8.09 (t, *J* = 8.06 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 10.66 (q), 21.06 (q), 21.14 (q), 27.20 (t), 30.63 (t), 41.27 (t), 43.31 (t), 44.92 (d), 49.01 (s), 53.59 (s), 80.91 (s), 125.47 (d), 142.67 (d), 155.15 (s). Anal. Calcd for $C_{27}H_{41}N_3O_8Zn$: C, 53.12; H, 7.16; N, 6.64; Zn, 10.33. Found C, 52.64; H, 7.23; N, 6.56; Zn, 10.25.

Complexation of $Zn(NO_3)_2$ with 2.7b

To a stirred solution of **2.7b** (0.25 g, 0.61 mmol) in 3 mL of chloroform was added $Zn(NO_3)_2.6H_2O$ (0.18 g, 0.61 mmol) and the mixture was stirred overnight. The formed solid was washed with chloroform and recrystallized from methanol/ethyl acetate by slow evaporation of the methanol affording the complex as colorless crystals (0.30 g, 0.51 mmol, 84%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.67 (s, 2H), 1.25 (m, 2H), 1.40 (m, 2H), 1.52 (m, 2H), 1.61 (m, 6H), 1.79 (m, 6H), 2.05 (m, 4H), 2.26 (m, 2H), 2.35 (m, 2H), 2.75 (s, 3H), 4.25 (s, 1H), 7.68 (d, *J* = 7.69 Hz, 1H), 7.95 (d, *J* = 7.69 Hz, 1H), 8.22 (dd, *J* = 7.69 Hz, *J* = 7.69 Hz, 1H); Anal. Calcd for $C_{27}H_{37}N_3O_8Zn$ C, 54.44; H, 6.27; N, 7.06. Found C, 54.24; H, 6.21; N, 7.01.

4.4b

The dithiol **3.1b** (0.12 g, 0.27 mmol) was dissolved in 5 mL of chloroform and a solution of $Zn(NO_3)_2.6H_2O$ (0.08 g, 0.27 mmol) in 5 ml of methanol was added the mixture was stirred overnight and filtered yielding the dimeric zinc complex **4.4b** (0.10 g, 0.21 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.4-1.8 (m, 20H), 1.92 (m, 1H), 2.18 (m, 1H), 2.36 (m, 2H), 2.59 (m, 2H), 3.05 (m, 1H), 3.12 (d, J = 14.3 Hz, 1H), 3.38 (d, J = 15.4 Hz, 1H), 4.01 (d, J = 15.4 Hz, 1H), 4.10 (d, J = 14.3 Hz, 1H), 7.29 (m 2H), 7.68 (m, 1H); Anal. Calcd for $C_{27}H_{35}NS_2Zn$ C, 64.65; H, 7.04; N, 2.79; Zn, 12.76. Found C, 64.34; H, 7.15; N, 2.75.

4.6

The dithiol **3.1b** (0.25 g, 0.57 mmol) was suspended in 5 mL of methanol and a solution of $ZnCl_2$ (76 mg, 0.57 mmol) in 5 mL of methanol was added. Stirring remained overnight and the mixture was subsequently filtered yielding the dimeric complex **4.4b** (80 mg, 0.16 mmol, 28%).

The solvent from the mother liquor was evaporated under high vacuum. Ethanol was added to obtain a soluble product in chloroform which was recrystallized from chloroform/hexane affording the complex **4.6** as colorless crystals (0.21 g, 0.29 mmol, 60%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, J = 7.1 Hz, EtOH), 1.6-2.0 (m, 20H), 2.26 (d, J = 12.0 Hz, 4H), 2.47 (d, J = 12.0 Hz, 4H), 3.52 (s, MeOH), 3.84 (s, 4H), 3.89 (q, J = 7.1 Hz, EtOH), 7.69 (d, J = 7.8 Hz, 2H), 8.28 (t, J = 7.8 Hz, 1H).

Crystal Structure of 4.6

*Crystal Data: Formula***:** $[C_{27}H_{38}NS_2]^+[ZnCl_3X]^-.CHCl_3$, where X = CH_2OH or C_2H_5OH, M = 770.08. Suitable transparent block-shaped crystals were obtained by recrystallization from chloroform. The crystal, a parallelepiped of approximate size 0.20 x 0.22 x 0.44 mm was used for data collection. The asymmetric unit consists of three moieties: a cationic ligand, a anionic Zn-complex and a chloroform solvent molecule. In the anionic Zn-complex the coordinated alcohol is a mixture of methanol / ethanol (56:44). The crystal was triclinic, $P\bar{}$, a = 10.622(2), b = 11.641(1), c = 15.032(1) Å, α = 87.359(9)°, β = 71.31(1)°, γ = 78.74(1)°, V = 1726.5(4) Å, Z = 2, D_x = 1.481 g cm^{-1}, λ(MoK$\bar{\alpha}$) = 0.71073 Å, μ = 13.2 cm^{-1}, F(000) = 799, T = 130 K. *Data collection*: The data were collected on an Enraf-Nonius *CAD*-4F^2 diffractometer (Mo tube, 50 kV, 40 mA, monochromated Mo-K$\bar{\alpha}$ radiation, Δω = 0.85 + 0.34 tg θ), range 17.85° < θ < 20.17°. Reflections collected: 7928 independent reflections: 7306. *Solutions and refinement*: The structure was solved by Patterson methods and extension of the model was accomplished by direct methods applied to difference structure factors using the program *DIRDIF*. $wR(F^2)$ = 0.0961 for 7306 reflections with $F_o^2 \geq 0$ and 532 parameters and $R(F)$ = 0.0364 for 6691 reflections obeying $F_o \geq 4.0\ \sigma(F_o)$ criterion of observability.

Table 4.6*: Interatomic distances and selected bond angles of* ***4.6*** **.**

Interatomic Distances (Å)					
S(1)[a]	-C(7)	1.840(2)[b]	Zn	-O(1)	2.018(2)
S(2)	-C(18)	1.845(2)	O(1)	-C(28)	1.399(4)
N(1)	-C(1)	1.351(3)	C(28)	-C(29)	1.492(8)
N(1)	-C(5)	1.347(3)	H(31)	-S(1)	1.21(4)
C(1)	-C(17)	1.495(3)	H(32)	-S(2)	1.26(3)
C(5)	-C(6)	1.494(3)	H(33)	-N(1)	0.87(3)
C(6)	-C(7)	1.559(3)	H(33)	-Cl(2)	2.35(3)
C(17)	-C(18)	1.556(3)	H(32)	-Cl(2)	2.73(3)
Zn	-Cl(1)	2.2114(9)	H(34)	-O(1)	0.74(3)
Zn	-Cl(2)	2.2425(8)	H(34)	-Cl(3)	2.32(3)
Zn	-Cl(3)	2.2536(8)	H(31)	-Cl(1)	2.909

Bond angles (deg.)							
C(1)	-N(1)	-C(5)	125.21(18)	Cl(3)	-Zn	-O(1)	108.08(6)
C(5)	-C(6)	-C(7)	114.26(17)	S(1)	-C(7)	-C(6)	107.28(14)
C(1)	-C(17)	-C(18)	115.38(18)	S(2)	-C(18)	-C(17)	107.63(14)
C(5)	-N(1)	-H(33)	117(2)	N(1)	-H(33)	-Cl(2)	167(3)
C(1)	-N(1)	-H(33)	118(2)	N(1)	-C(1)	-C(17)	117.65(18)
C(28)	-O(1)	-H(34)	107(2)	N(1)	-C(5)	-C(6)	117.84(18)
Cl(2)	-Zn	-O(1)	101.94(6)	H(31)	-S(1)	-C(7)	93(2)
Cl(1)	-Zn	-Cl(2)	116.43(3)	H(32)	-S(2)	-C(18)	95(3)
Cl(1)	-Zn	-Cl(3)	115.17(3)	Zn	-O(1)	-C(28)	124.89(18)
Cl(1)	-Zn	-O(1)	102.45(6)	Zn	-O(1)	-H(34)	122(2)
Cl(2)	-Zn	-Cl(3)	111.10(3)				

[a] The numbering for the crystal data does not follow the numbering used in nomenclature.

[b] Standard deviation in parentheses.

4.5f

To a solution of dithiol **3.1f** (0.25 g, 0.56 mmol) in 5 mL of chloroform was added $Zn(NO_3)_2.6H_2O$ (0.17 g, mmol) in 5 mL of methanol. The mixture was stirred overnight filtered and concentrated in vacuo yielding the complex **4.4f** as a white solid (0.17 g, 0.34 mmol, 60%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.68 (s, 6H), 1.2-1.8 (m, 22H), 1.96 (d, J = 10.4 Hz, 2H), 2.64 (m, 2H), 3.49 (m, 2H), 3.66 (m, 2H), 7.17 (d, J = 7.7 Hz, 2H), 7.61 (t, J = 7.7 Hz, 1H). HRMS calcd 505.182, found 505.183. Anal. Calcd for $C_{27}H_{39}NS_2Zn$: C, 63.95; H, 7.75; N, 2.76. Found C, 63.65; H, 7.65; N, 2.86 .

Complexation of 3.1f with $Co(NO_3)_2$

To a solution of dithiol **3.1f** (0.22 g, 0.50 mmol) in 5 mL of chloroform was added $Co(NO_3)_2.6H_2O$ (0.15 g, 0.50 mmol). After stirring for 1.5 h the mixture was stored at –20 °C overnight. A purple solid was formed and filtered affording the dimeric complex (0.09 g, 0.18 mmol, 35%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.43 (s, 3H), 0.60 (s, 3H), 1.1-1.4 (m, 16H), 1.7 (m, 8H), 1.98 (m, 1H), 2.44 (m, 1H), 2.82 (d, J = 15.3 Hz, 1H), 2.98 (d, J = 14.1 Hz, 1H), 3.27 (d, J = 14.1 Hz, 1H), 3.35 (d, J = 15.3 Hz, 1H), 6.65 (d, J = 7.7 Hz, 1H), 7.28 (m, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.61 (t, J = 7.7 Hz, 1H). Anal. Calcd for $C_{27}H_{39}NS_2Co$: C, 64.77; H, 7.85; N, 2.80. Found C, 64.55; H, 7.74; N, 2.90.

4.8 References.

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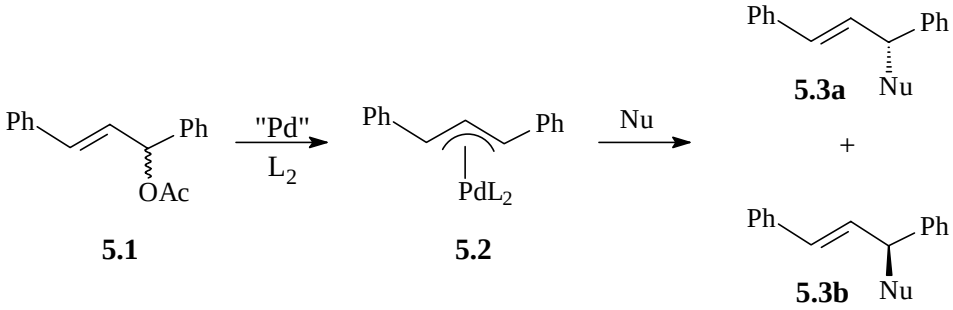
CHAPTER 5

Pyridine Sulfides as Ligand in Palladium-Catalyzed Allylic Substitution.*

Abstract: The asymmetrical pyridine thiol **3.11f** and the C_2-symmetrical pyridine dithiol **3.1f** were tested in the palladium-catalyzed allylic substitution, a well-studied reaction in asymmetric catalysis. Comparison of the results with these ligands could give more insight in the structural aspects of this reaction. It was found, however, that the thiol groups of these ligands, which are readily deprotonated by the base, inactivate the metal catalyst. Alkylation of these pyridine thiols followed by complexation to the metal led to active catalysts with enantioselections of 46-92% for the palladium-catalyzed allylic substitution. For the asymmetric thioethers **5.4** the bulkiness of the alkyl chain seems to have a large impact on the ee, whereas for the C_2-symmetrical thioethers **5.5** the impact is smaller. The best result was obtained with the asymmetric pyridine benzyl thioether (-)-**5.4e**. Optimization of the reaction conditions led to an enantioselectivity of 98% with a ligand of the same optical purity ((+)-**5.4e**). In other words the enantioselection is absolute. Mechanistic insight was gained by studying the allylic intermediate of the asymmetric thioether (+)-**5.4d**. NMR spectral data (^{1}H, *NOESY*, *COSY*) were consistent with the presence of more then one isomer, whereas X-ray diffraction of an isolated crystal revealed a single isomer. Clearly the structure in solution is dynamic. Translation of the experimental data for the isolated intermediate to the catalytic reaction required the assumption of a large influence of the methyl group on the pyridine ring. Laboratory experiments established that the absence of this methyl group indeed has a dramatic and negative impact on the enantioselection. Attempts to isolate the allylic intermediate with the bisthioether failed because of the instability of the complex. In this case C_2-symmetrical complex of the bisthioether with palladium chloride was isolated.

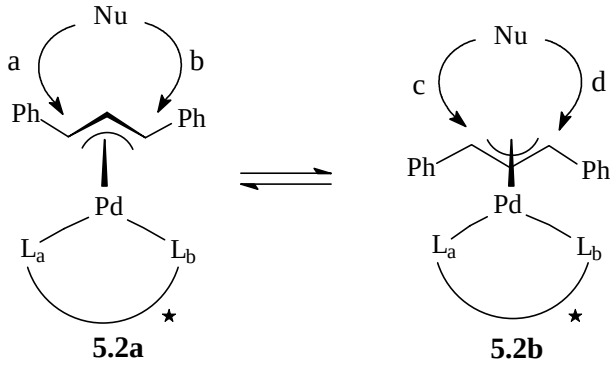
5.1 Introduction.

One of the more successful approaches to catalytic asymmetric carbon-carbon bond formation is by means of transition-metal catalysis.[1] In particular, palladium-catalyzed allylic substitution is a well-studied reaction, which has been used to demonstrate chemo-, regio-, diastereo- and enantioselectivity.[2] Because the reaction is reasonably well understood, palladium-catalyzed substitution on racemic 1,3-diphenylprop-2-enyl acetate **5.1** with malonate esters (Nu in Scheme 5.1) is an excellent model for testing design principles of asymmetric ligands.



Scheme 5.1 *Palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate.*

A commonly used approach to the control of enantioselectivity in transition metal catalyzed reactions is based upon the use of ligands possessing only rotational symmetry elements[3]. With some exceptions, C_2-symmetrical ligands seem to be most successful. Introduction of C_2-symmetry allows reduction of the number of different reaction pathways. This is illustrated in Scheme 5.2. The nucleophile adds to the π-allyl palladium intermediate **5.2,** which in the absence of symmetry elements actually consists of two isomers **5.2a** and **5.2b,** which are in equilibrium through π-σ-π isomerization. Each intermediate has two possible entry pathways (a,b) or (c,d) for the nucleophile.



Scheme 5.2 *Palladium allyl intermediates.*

When non-symmetrical auxiliaries ($L_a \neq L_b$) are used all four entry pathways to the transition states of the two isomers of intermediate **5.2** can contribute, whereas the use of C_2-symmetrical auxiliaries ($L_a = L_b$; chirality is still embedded in the backbone of the ligand) reduces the number of entry pathways to two (a=d and b=c).

On the other hand previous work has demonstrated that the reactivity of the terminal carbon atoms of the allyl moiety in the palladium-allyl complex depends upon the kind of ligand that coordinates to the metal.[4] Phosphites and phosphines are strongly π accepting and therefore enhance reactivity, whereas nitrogen ligands, which are poorer π acceptors, form less reactive species. Combining two ligating atoms of non-identical π acceptor capacity in one compound leads to an asymmetrical η^3-allyl complex. Attack of the nucleophile is expected to take place *trans* to the best π-acceptor, since the better π-acceptor is able to withdraw electron density from the position *trans* to itself, and induce greater electron deficiency at this allylic terminus. The nucleophilic substitution product **5.3a** will be formed if the nucleophile enters (attack from backside of allyl system as drawn) through path a or d and the product **5.3b** when the reaction proceeds through path b or c (Scheme 5.2). If L_b is the best π-acceptor, attack through path a and c is favored and asymmetric induction will be achieved if the equilibrium between two possible intermediates of **5.2** can be shifted selectively to either the right or the left. Although nonsymmetrical bidentate ligands allow more permutations, the character of the ligands themselves can provide the means of control by exclusion of possible entry pathways based on the π-acceptor ability of the ligating atoms.

Design and development of ligands, both C_2-symmetric and not, has focused mainly on chiral nonracemic phosphorus-containing ligands and has led to, for example, BINAPO by *Trost*[5], the ferrocenyl phosphites employed by *Hayashi*[6] and *Togni*,[7] QUINAP by *Brown*[8] and more recently, the monophosphines by *Zhang*.[9] Well-defined structural elements in the rigid complexes ensure high chiral recognition.

A practical difficulty with such ligands is, in many cases, high sensitivity to oxidation by oxygen. Less oxidation sensitive amines and sulfides are also capable of stabilizing the low-valent state of palladium, and recently, some interest has shifted in the direction of non-phosphorus-containing ligands. Some examples of non-phosphorus-containing ligands, which are both catalytically active and give good chiral recognition, are sparteine[10] and stilbenediamine derivatives,[11] semicorrins and bisoxazolines,[12] ephedra-based amino sulfides,[13] sulfur-containing oxazoline ligands,[14] (hydroxyalkyl)-pyridino-oxazolines,[15] C_2-symmetrical bis(aziridines),[16] and more recently, bis(oxazolinylpyridinyl)-dioxolanes.[17]

Sulfides form a good perspective for development of new ligands, since sulfur is a soft complexation site and palladium is a soft metal ion, factors, which will generally lead to a strong complex. Furthermore, back-donation of π-electron density from the metal to the

empty relatively low-energy d orbitals of the sulfur can contribute to the strength of the Pd(II)-S bond.[18] In contrast to *trivalent* phosphines and phosphites, *divalent* sulfide cannot be intrinsically chiral. On complexation to a metal, chirality can be induced at sulfur. However, the difficulty in controlling this aspect is likely the reason that few sulfur-containing ligands have been reported or used. However, as described in chapter 3, a new method for the easy preparation of C_2-symmetrical chiral "pyridine dithiols" (condensation products of 2,6-lutidine with two equivalents of thiofenchone) has been developed.[19] "Single armed" pyridine thiol (+)-**3.11f** intermediates in this reaction are also of interest. We anticipated that on use of structurally rigid thioketones a variety of thiol- or sulfide-containing ligands could be obtained in which the coordination geometry is defined at the outset. To obtain insight in the structural aspects in the palladium catalyzed allylic substitution, the pyridine thiol and dithiol form good starting points for mechanistic studies on the geometry of the intermediate **5.2**. With the use of the pyridine thiol (+)-**3.11f** and the dithiol **3.1f** the control of stereoselection by C_2-symmetrical vs. non-symmetrical bidentate ligands was studied.

5.2 Palladium-Catalyzed Allylic Substitution.

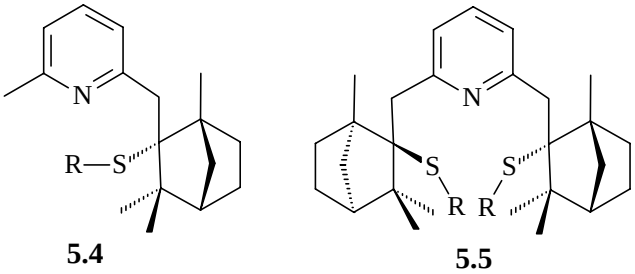
In initial experiments, thiols (+)-**3.11f** and **3.1f** were used as ligands in the palladium-catalyzed alkylation of 1,3-diphenylprop-2-enyl acetate **5.1**. These experiments were carried out in dry dichloromethane at room temperature in the presence of $[(\eta^3C_3H_5)PdCl]_2$ and the ligand. The nucleophile was generated either from dimethyl malonate in the presence of bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate or from dimethyl malonate and sodium hydride. With sodium hydride as base, very low conversions and low to moderate selectivities were found after 36 h (Table 5.1).

Table 5.1: *Test results with thiols* (+)-***3.11f*** *and* ***3.1f***.

Ligand	base	equiv. of base/ NuH	Yields (%)	ee[a] (%)	confgn[a]
(+)-**3.11f**	NaH	1.5/1.5	2	80	S
3.1f	NaH	1.5/1.5	4	23	R
(+)-**3.11f**	BSA/KOAc	1.2/1.5	10	81	S
3.1f	BSA/KOAc	1.2/1.5	-	-	-

[a] The enantiomeric excess was determined by ^{1}H NMR using Eu(hfc)$_3$ as chiral shift reagent, and the absolute configurations were established by comparing the optical rotation with literature values for material of established absolute configuration. [12, 20] **General Procedure**: $[(\eta^3C_3H_5)ClPd]_2$ (0.01 mmol), ligand (0.02 mmol), **5.1** (1.0 mmol) in dichloromethane. Sodium dimethylmalonate (1.5 mmol) in 5 mL of dichloromethane was added. Stirred for 18 h at RT.

Using BSA as base resulted in an increase in yield for (+)-**3.11f**, however, no product was found when **3.1f** was used. The low reactivity with these ligands is probably due to deprotonation of the thiol group by the bases. In order to bypass problems arising from the reactivity of the thiol groups, we converted thiols (+)-**3.11f** and **3.1f** to their thioethers **5.4** and **5.5**. For the preparation of the methyl thioethers, K_2CO_3 was used as base and methyl iodide as the methylating reagent; the mono and dithioether adduct were obtained in 76% and 94% yields for (+)-**5.4a** (R = CH_3) and **5.5a** (R = CH_3) respectively. For the preparation of the homochiral series ethyl, *iso*-propyl, *n*-propyl, and benzyl thioethers (+)-**5.4b-d** and (–)-**5.4e** and **5.5b-e** sodium hydride was used to deprotonate the thiol. These thioethers were isolated in 50-89% yield.



5.4 **5.5**

*Structures **5.4** and **5.5***

Table 5.2: *Test results with thioethers* (+)-***5.4a-d,*** (–)-***5.4e*** *and* ***5.5***.

ligand	R	base	equiv. of base/NuH	Yields (%)	ee[a] (%)	confgn[a]
(+)-**5.4a**	Me	NaH	1.5/1.5	35	46	R
(+)-**5.4b**	Et	NaH	1.5/1.5	70	81	R
(+)-**5.4a**	Me	BSA/KOAc	1.2/1.5	80	53	R
(+)-**5.4b**	Et	BSA/KOAc	1.2/1.5	84	91	R
(+)-**5.4c**	i-Pr	BSA/KOAc	1.2/1.5	93	82	R
(+)-**5.4d**	n-Pr	BSA/KOAc	1.2/1.5	90	81	R
(–)-**5.4e**	benzyl	BSA/KOAc	1.2/1.5	96	92	R
5.5a	Me	BSA/KOAc	1.2/1.5	83	78	R
5.5b	Et	BSA/KOAc	1.2/1.5	80	84	R
5.5c	n-Pr	BSA/KOAc	1.2/1.5	89	85	R
5.5d	i-Pr	BSA/KOAc	1.2/1.5	80	85	R
5.5e	benzyl	BSA/KOAc	1.2/1.5	90	85	R

[a] The enantiomeric excess was determined by ^{1}H NMR using Eu(hfc)$_3$ as chiral shift reagent, and the absolute configurations were established by comparing the optical rotation with literature values for material of established absolute configuration.[12,20] **General Procedure**: [(η^3C$_3$H$_5$)ClPd]$_2$ (0.01 mmol), ligand (0.02 mmol), **5.1** (1.0 mmol) in dichloromethane. Dimethylmalonate (1.5 mmol), N,O-bis(trimethylsilyl)acetamide (1.2 mmol) and anhydrous potassium acetate (30 µmol) were added. The mixture was stirred for 10 h at RT.

The initial experiments in the palladium catalyzed allylic substitution were carried out with thioethers (+)-**5.4a** and (+)-**5.4b** using NaH as base to deprotonate the malonate. These experiments afforded the product **5.3** in 35 and 70% isolated yield and 46 and 81% ee for (+)-**5.4a** and (+)-**5.4b,** respectively, after a reaction time of 18 h. Using BSA as base, higher selectivities and conversions were found for these ligands at shorter reaction times (10 h). The next step was application of BSA as base in combination with the other thioethers (+)-**5.4c**-**d,** (–)-**5.4e** and **5.5a**-**e**. The reactions proceeded smoothly and were complete within 10 h. The product **5.3** was obtained in high yield and in moderate to high enantiomeric excess as summarized in Table 5.2.

The benzyl thioethers (–)-**5.4e** and **5.5e** were found to perform best under these conditions, and these ligands were selected for optimization of the allylic substitution (Table 5.3). Replacement of dichloromethane by acetonitrile led to an increase of the enantioselectivity when (–)-**5.4e** was used. The enantioselectivity using (–)-**5.4e** was further optimized by using 3 equiv. of base and nucleophile together with lower reaction temperature. For (–)-**5.4e** this is theoretically the highest enantioselectivity that could be obtained since the starting material (*R*)-(–)-fenchone can only be purchased in 96% enantiomeric purity. We therefore synthesized ligand (+)-**5.4e** under the same conditions used for (–)-**5.4e** starting from pyridine thiol (–)-**3.11f** (synthesized from the more expensive (*S*)-(+)-fenchone, which can be purchased in 98% enantiomeric purity). Application of (+)-**5.4e** in the allylic substitution reaction afforded the product **5.3** in 96% isolated yield and 98% ee. No notable increase in the selectivity was found when **5.5e** was applied under the optimized conditions.

Table 5.3: *Optimization with thioethers* (–)-***5.4e***, (+)-***5.4e, and 5.5e.***

Ligand	R	T (°C)	solvent	base	equiv. of base/NuH	Yields (%)	e.e.[a] (%)	confgn[a]
(–)-**5.4e**	benzyl	rt	CH_3CN	BSA/KOAc	1.2/1.5	94	93	R
(–)-**5.4e**	benzyl	0 °C	CH_3CN	BSA/KOAc	1.2/1.5	96	95	R
(–)-**5.4e**	benzyl	0 °C	CH_3CN	BSA/KOAc	3/3	95	96	R
(+)-**5.4e**	benzyl	0 °C	CH_3CN	BSA/KOAc	3/3	96	98	S
5.5[e]	benzyl	0 °C	CH_3CN	BSA/KOAc	3/3	75	86	R

[a] The enantiomeric excess was determined by ^1H NMR using $Eu(hfc)_3$ as chiral shift reagent, and the absolute configurations were established by comparing the optical rotation with literature values for material of established absolute configuration.[12,20] **General Procedure**: $[(\eta^3C_3H_5)ClPd]_2$ (0.01 mmol), ligand (0.02 mmol), **5.1** (1.0 mmol) in dichloromethane. Dimethylmalonate (1.5 mmol), N,O-bis(trimethylsilyl)acetamide (1.2 mmol) and anhydrous potassium acetate (30 µmol) were added. The mixture was stirred for 10 h at RT.

5.3 Causes of Induction of Chirality and Comparison with C_2-symmetrical Ligands.

In order to obtain more insight in the reaction mechanism and the mechanism of introduction of chirality into the product, the allylic intermediate **5.6** was synthesized. This complex was prepared from (+)-**5.4c** and $[(\eta^3C_3H_5)PdCl]_2$ using $AgPF_6$ to replace the chloride. The ^{1}H NMR spectrum showed a mixture of the two diastereomeric complexes **5.6a** and **5.6b** in which the allylic moiety is coordinated either *exo* or *endo* to the palladium relative to the thioether. The ratio between the two diastereomeric complexes was determined to be 3:4 at 20.0 °C. Temperature-dependent studies of this complex showed an increase in the preference for **5.6b** as the temperature decreased. Elucidation of the ^{1}H NMR spectrum was accomplished by *COSY* (Figure 5.1) and *NOESY* (Figure 5.2) experiments.

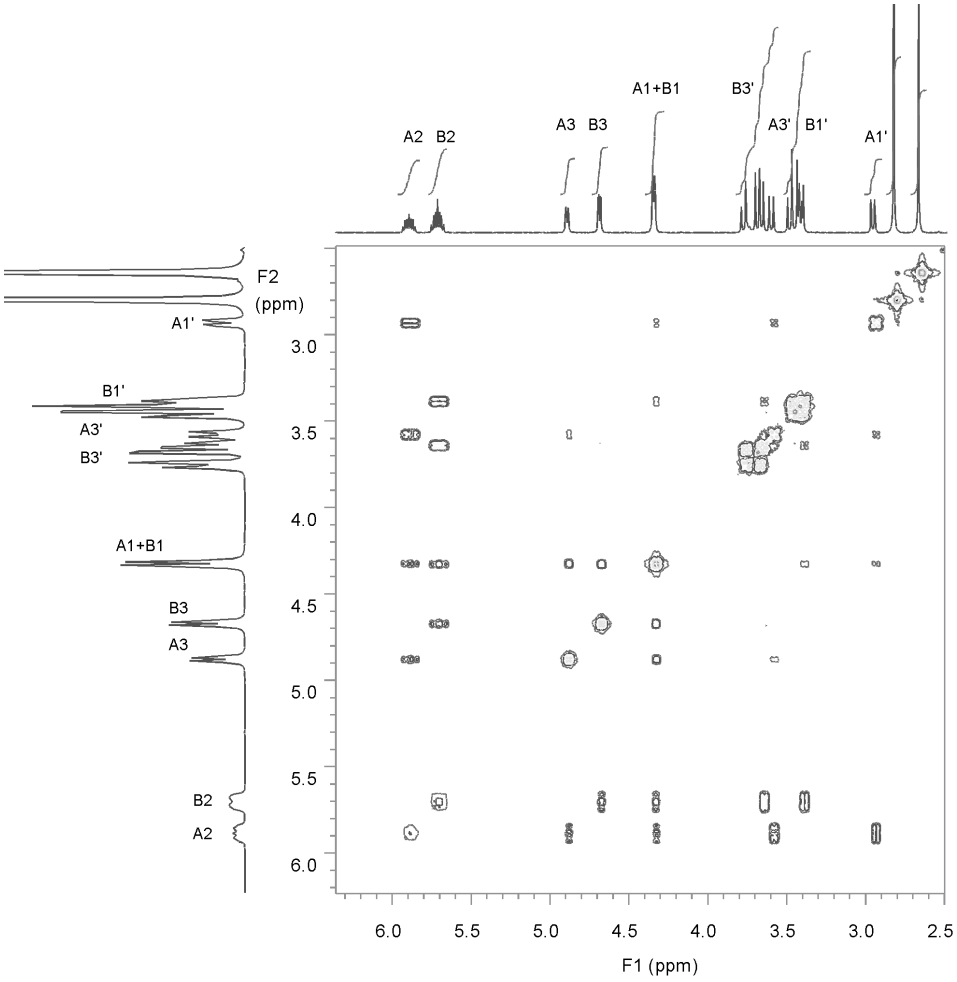


Figure 5.1: *COSY spectrum from **5.6.***

From the integrals of the specific signals and from the *COSY* experiments, we could assign the signals at δ 2.94, 3.58, 4.33, 4.88, and 5.88 as belonging to the minor diastereomer and the signals at δ 3.39, 3.65, 4.33, 4.68, and 5.70 to the major diastereomer. The signals in the ^{1}H NMR spectrum at δ 5.70 and 5.88 correspond to the protons H_2 of the diastereomeric

complexes as was deduced from their couplings, chemical shifts and *COSY* interactions. Assuming that the coupling constant between H_2 protons and the protons *cis* to H_2 is smaller than the coupling between the *trans* protons we assigned the signals at δ 4.33, 4.68, and 4.88 to the protons *cis* relative to H_2. The signals at δ 2.94, 3.39, 3.58, and 3.65 were assigned as the protons *trans* to the H_2 protons. Remarkable in the spectrum is that there is no geminal coupling between the protons of the terminal CH_2 group of the allylic moiety, as is also found for the geminal protons in the $[(\eta^3C_3H_5)PdCl]_2$ complex.[21] Since the protons H_3 of the allylic moiety *trans* to the sulfur atom are slightly less electron rich due to the electron-withdrawing character of the sulfur, they will adsorb at lower field than the H_1 protons *trans* to nitrogen, and therefore they could be assigned as the signals at δ 4.68 and 4.88. The signal at 4.33 corresponds therefore to the H_1 protons of both diastereomers. Likewise, the signals at δ 3.58 and 3.65 correspond to the protons $H_{3'}$ *trans* to the sulfur atom and the signals at δ 2.94 and 3.49 correspond to the protons $H_{1'}$.

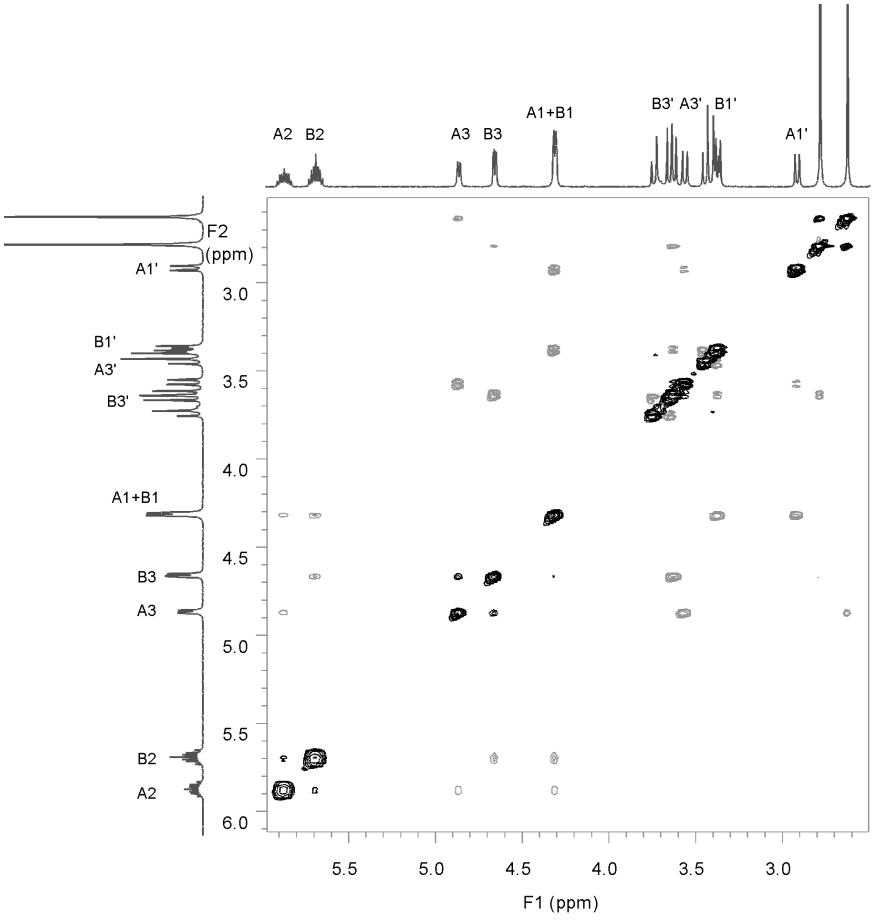


Figure 5.2: *NOESY spectrum from* ***5.6.***

More information about the complex was obtained from the X-ray diffraction (Figure 5.3). Only the minor isomer corresponding to structure **5.6a** crystallized from the mixture. At first it was assumed that the structure of the major diastereomer had been determined. *NOESY*

experiments, however, gave convincing data to suppose otherwise. In the *NOESY* spectrum, we observed an interaction between H_{3a} of the allyl group (δ 4.88) and the 6-methyl group of the pyridine ring (Me_a; δ 2.64) and an interaction between $H_{1a'}$ (δ 2.94) and one of the methyl groups from the fenchone moiety (δ 1.41). From these interactions, we concluded that this is the structure that is found in the crystal since herein the H_{3a} proton is adjacent to the methyl group and the $H_{1a'}$ is positioned closely to the fenchone methyl group. The minor diastereomer thus corresponds to structure **5.6a**. For the major diastereomer, we find an *NOE* interaction for $H_{3b'}$ (δ 3.65) with the pyridine methyl group (Me_b; δ 2.80) and an *NOE* interaction between H_{1b} (δ 4.33) and one of the methyl groups from the fenchone moiety (δ 1.30), indicating that this corresponds to structure **5.6b**.

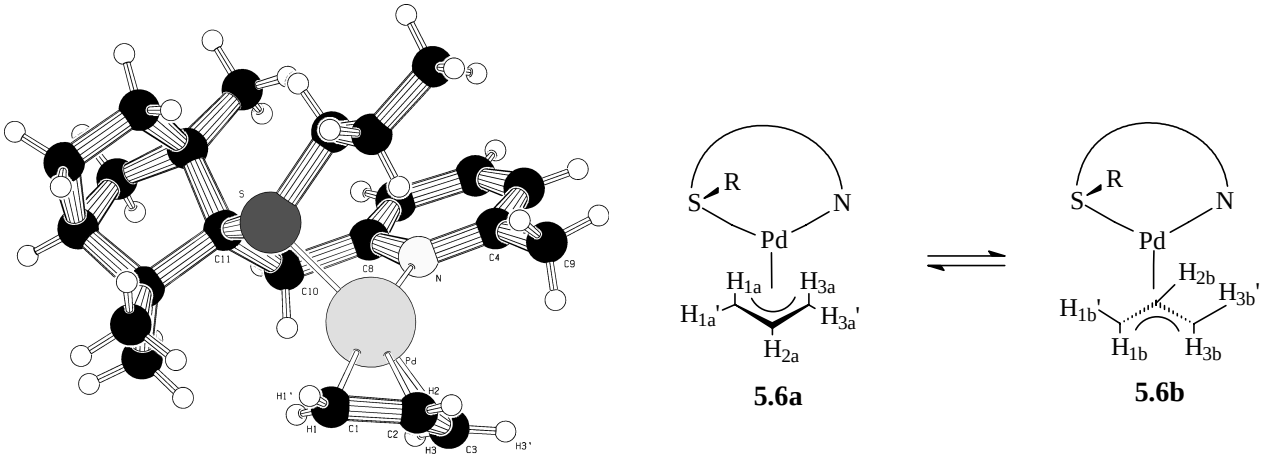
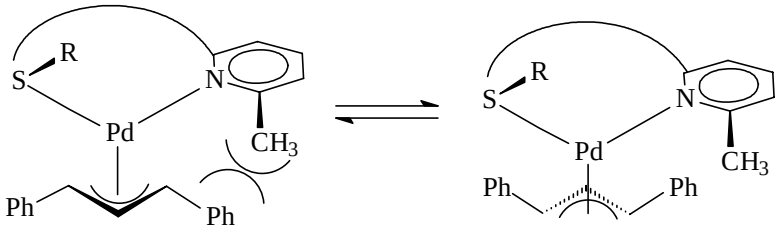


Figure 5.3 *X-ray structure of **5.6a** without the counter ion PF_4^-.; and structures **5.6a** and **5.6b**.*

In the crystal structure, the palladium is coordinated to the sulfur, the nitrogen atom, and C_1, C_2, and C_3 of the allylic moiety embedded in a square-planar coordination for palladium. The bond length of Pd-C_3 (*trans* to sulfur) is somewhat longer than the Pd-C_1 bond length because of the π-accepting ability of the sulfur, making the C_3-atom more electron deficient. Therefore, nucleophilic attack will take place at this carbon center.

The yields of the allylic substitution are good, the reaction times are acceptable, and the ee's of the optimized reactions are virtually absolute. The thioethers (+)-**5.4a-d** and (–)-**5.4e** constantly provide substitution product **5.3** of R absolute configuration. The bulk of the substituent on sulfur has a moderate correlation with improved enantiomeric excesses. The structure of the complex **5.6a** (Figure 5.3) confirms our expectation that sulfide is rigidly coordinated in a six-membered ring and that the fenchyl methyl groups force a single absolute configuration, in this case S, on the coordinated sulfur. The isolated methyl group at the 6-position of the pyridine ring plays a key role in determining the orientation of the π-allyl

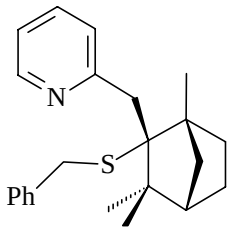
complex; one end of the allyl group is forced against the steric bulk of the fenchyl methyls, whereas the 6-methyl group exerts controlling influence on the other end of the allyl group. We believe that for the 1,3-diphenylallyl group used here these interactions enforce structure **5.7b** rather than **5.7a** in which the phenyl groups are oriented toward the steric bulk on both sides. Attack of the malonate nucleophile should logically occur away from the greatest steric bulk, in other words on the side of the pyridine ring bearing only the 6-methyl group. This is on electronic grounds also expected since the soft nucleophile attacks *trans* to the softer sulfide, which is the better π acceptor. This leads to the observed R configuration of **5.3**.



5.7a **5.7b**

*Structures **5.7a** and **5.7b***

The role of the methyl group at the 6-position of the pyridine ring is readily demonstrated to be profound. Compound **5.9** lacking the 6-methyl group was prepared. Allylic substitution proceeded readily, and **5.3** was obtained in good yield but only in 47% ee and *as the S enantiomer*.



5.9

*Structure **5.9***

Clearly control over the manner of complexation has been lost by elimination of this small but essential methyl group. Similar effects of substituents of 6-substituted vs. 6-unsubstituted pyridines was also reported by Chelucci.[22]

When the C_2-symmetrical dithioethers **5.5** are used as ligand, the chemical yields and the enantioselectivities are still high. The substituents R on the sulfur do not have a great impact on the stereoselectivity of the reaction, whereas for the ligands (+)-**5.4a-d** and (–)-**5.4e** there is a reasonable correlation between the size of the substituent R and the ee of **5.3** (Table 5.2).

To obtain more insight into the induction of chirality, we attempted to isolate the Pd-allylic intermediate of **5.5e** and $[(\eta^3C_3H_5)PdCl]_2$. However, a product was isolated, which was characterized by *COSY* and ^{1}H NMR as being fully symmetrical but devoid of allyl group (Figure 5.4). The ligand is unambiguously coordinated as can be seen in the downfield shift of the pyridine protons and the increase in coupling between the two diastereotopic benzylic protons of the thioether. The observation that the system still exhibits a C_2-symmetry is proof

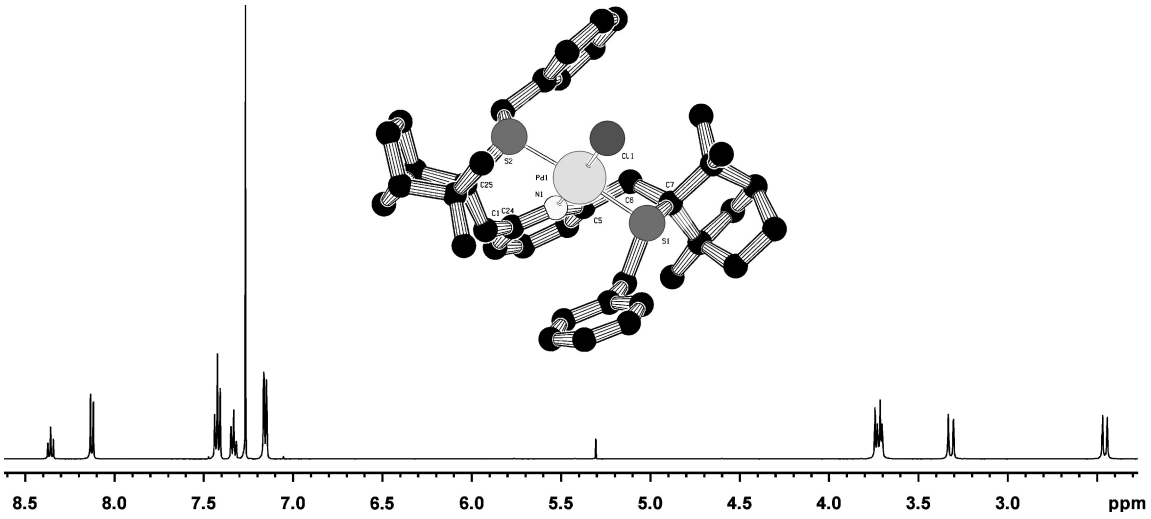


Figure 5.4 *X-ray structure and ^{1}H NMR spectrum of **5.10** (X-ray shown without the counter ion BF_4^-).*

for the complexation of the palladium to both sulfur atoms; otherwise, an asymmetrical system would have been obtained. Recrystallization of this complex from dichloromethane by isothermal distillation of hexane into the solution afforded the Pd-Cl complex **5.10** as BF_4^- salt as was established by X-ray diffraction (Figure 5.4). The palladium-allyl complex involved in reaction seems to be too labile and degrades to **5.10**. This instability has thwarted all subsequent attempts to obtain the desired palladium-allyl complex. The palladium chloride complex **5.10** exhibits square-planar coordination of the palladium to the sulfur and nitrogen atoms. Speculations for the explanation of the stereochemical outcome for the dithioethers without knowing the active catalytic species are inappropriate.

5.4 Conclusions.

The results obtained with the C_2-symmetrical pyridine dithioethers and with the non-symmetrical bidentate pyridine thioethers show that for these systems enantioselection can be controlled more easily with the bidentate ligands rather then the C_2-symmetrical ligands. Moreover discrimination between the four possible entry pathways for the nucleophile (a-d;

$L_a \neq L_b$) is easier controlled then the discrimination between the two possible entry pathways with C_2-symmetrical ligands (a=d, b=c; $L_a=L_b$) for these type of ligands (Scheme 5.2).

In these easily accessible systems, we have found a new class of ligands for the palladium-catalyzed allylic substitution reaction. The optimized results with the monothioethers can scarcely be improved in terms of yield and ee. The possibility of introducing other groups at the 6 position of the pyridine ring (such as *tert*-butyl) give these systems high potential for other catalytic applications.

5.6 Experimental Section.

General Remarks: See chapter 2.

General Procedure for the palladium catalyzed allylic substitution with NaH.
To $[(\eta^3C_3H_5)ClPd]_2$ (0.01 mmol) in 2 mL of dry dichloromethane was added the ligand (0.02 mmol). The suspension was degassed at 0.1 mm Hg by three freeze-thaw cycles. The mixture was stirred for 30 min at RT and 1,3- diphenyl-2-enyl acetate **5.1** (0.25 g, 1.0 mmol) in 2 mL of dry dichloromethane was added. The mixture was degassed again by three freeze-thaw cycles and stirring continued for an additional half hour. Sodium dimethylmalonate (freshly prepared from dimethylmalonate (0.20 g, 1.5 mmol) and sodium hydride (0.07 g, 1.5 mmol) in 5 mL of dichloromethane) was added. The mixture was immediately degassed by three freeze-thaw cycles and allowed to stir for 18 h at RT. The mixture was quenched with 2N NH_4Cl and extracted twice with diethyl ether. The organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure the product was purified by means of column chromatography (silica, hexane/ethyl acetate (3:1)) yielding **5.3** as a white solid.

General Procedure for the palladium catalyzed allylic substitution with BSA.
To $[(\eta^3C_3H_5)ClPd]_2$ (0.01 mmol) in 2 mL of dry dichloromethane was added the ligand (0.02 mmol). The suspension was degassed at 0.1 mm Hg by three freeze-thaw cycles. The mixture was stirred for 30 min at RT and 1,3- diphenyl-2-enyl acetate **5.1** (0.25 g, 1.0 mmol) in 2 mL of dry dichloromethane was added. The mixture was degassed again by three freeze-thaw cycles and stirring continued for an additional half hour. Dimethylmalonate (0.20 g, 1.5 mmol), N,O-bis(trimethylsilyl)acetamide (0.24 g, 1.2 mmol) and anhydrous potassium acetate (3 mg, 30 µmol) were added. The mixture was immediately degassed by three freeze-thaw cycles and allowed to stir for 10 h at RT. Workup was followed as above.

General Procedure A for the Synthesis of Thioethers (+)-**5.4a and 5.5a.** To 1.0 mmol of thiol or dithiol adduct, dissolved in 50 mL of acetone, were added K_2CO_3 (1.5 equiv.) and iodomethane (2.0 equiv.). The mixture was stirred at reflux conditions overnight. After being

cooled to rt the mixture was filtered and the solvent evaporated. The product was purified by means of column chromatography (silica gel, hexane/diethyl ether 6:1).

General Procedure B for the Synthesis of Thioethers 5.4 and 5.5. To 1.0 mmol of thiol or dithiol adduct, dissolved in 50 mL of THF, was added sodium hydride (1.5 equiv.) and stirring continued for 10 min. To this solution was added the alkyl halide (1.5 equiv.) and stirring continued overnight at rt. Water (10 mL) was added, and the mixture was extracted twice with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by means of column chromatography (silica gel, hexane/diethyl ether 6:1).

2-Methyl-6-[[(1*R*,2*R*)-1,3,3-trimethyl-2-(methylsulfanyl)bicyclo[2.2.1]hept-2-yl]methyl]pyridine (+)-**5.4a.** This compound was prepared according to general procedure A starting from (+)-**3.11f** (0.50 g, 1.82 mmol), K_2CO_3 (0.37 g, 2.7 mmol), and iodomethane (0.51 g, 3.6 mmol) to yield a colorless solid that was recrystallized from hexane (0.40 g, 1.38 mmol, 76%): mp 65-67 °C; $[\alpha]^{23}_D$ +21 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 0.87 (s, 3H), 1.15 (s, 3H), 1.18 (s, 3H), 1.2 (m, 2H), 1.37-1.55 (m, 2H), 1.7 (m, 1H), 1.98 (s, 3H), 2.04 (m, 1H), 2.53 (s, 3H), 2.6 (m, 1H), 3.34 (dd, *J* = 17.57 Hz, *J* = 22.96 Hz, 2H), 6.94 (d, *J* = 7.57 Hz, 1H), 7.48 (dd, *J* = 7.57 Hz, *J* = 8.05 Hz, 1H), 8.20 (d, *J* = 8.05 Hz, 1H); ^{13}C NMR δ 13.58 (q), 20.07 (q), 24.23 (q), 24.49 (q), 24.68 (t), 29.44 (q), 34.61 (t), 41.39 (t), 41.99 (t), 46.78 (s), 51.11 (d), 56.15 (s), 60.78 (s), 120.20 (d), 120.52 (d), 135.99 (d), 156.73 (s), 160.82 (s); HRMS calcd. 289.185, found 289.186. Anal. Calcd. for $C_{18}H_{27}NS$: C, 74.69; H, 9.40; S, 11.08. Found C, 74.93; H, 9.44; S, 11.05.

2-Methyl-6-[[(1*R*,2*R*)-1,3,3-trimethyl-2-(ethylsulfanyl)bicyclo[2.2.1]hept-2-yl]methyl]pyridine (+)-**5.4b.** For this compound, general procedure B was used, starting from (+)-**3.11f** (0.50 g, 1.82 mmol), sodium hydride (0.09 g, 3.6 mmol), and ethyl bromide (0.29 g, 2.7 mmol). (+)-**5.4b** was obtained as a colorless solid after Kugelrohr distillation (0.5 mmHg, 150 °C) (0.43 g, 1.42 mmol, 78%): mp 65-66 °C; $[\alpha]^{23}_D$ +10 (*c* 7.8, $CHCl_3$); ^{1}H NMR δ 0.87 (s, 3H), 1.12 (t, *J* = 7.57 Hz, 3H), 1.16 (s, 3H), 1.18 (s, 3H), 1.20-1.26 (m, 2H), 1.37-1.43 (m, 1H), 1.50-1.60 (m, 1H), 1.7-1.8 (m, 1H), 2.00 (d, *J* = 10.7 Hz, 1H), 2.3 - 2.4 (m, 1H), 2.51 (s, 3H), 2.55-2.7 (m, 2H), 3.25 (d, *J* = 17.6 Hz, 1H), 3.44 (d, *J* = 17.6 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 7.49 (dd, *J* = 7.8 Hz, *J* = 7.6 Hz, 1H), 8.23 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR δ 13.67 (q), 19.91 (q), 23.52 (t), 24.25 (q), 24.74 (t), 29.31 (q), 34.70 (t), 41.78 (t), 42.31 (t), 46.84 (s), 51.07 (d), 56.10 (s), 61.94 (s), 120.09 (d), 120.61 (d), 135.85 (d), 156.63 (s), 160.97 (s); HRMS calcd. 303.203, found 303.202. Anal. Calcd. for $C_{19}H_{29}NS$: C, 75.19; H, 9.63; N, 4.61. Found C, 75.12; H, 9.64; N, 4.57.

2-Methyl-6-[[(1*R*,2*R*)-1,3,3-trimethyl-2-(*iso*-propylsulfanyl)bicyclo[2.2.1]hept-2-yl]methyl]pyridine (+)-**5.4c.** This material was synthesized according to the general procedure B starting from (+)-**3.11f** (0.50 g, 1.82 mmol), sodium hydride (0.09 g, 3.6 mmol) and *iso*-propylbromide (0.33 g, 2.7 mmol). The product was obtained after Kugelrohr distillation (0.5 mmHg, 160 °C) as a colorless solid (0.50 g, 1.58 mmol, 87%): mp 47-48 °C; $[\alpha]^{23}_{D}$ +40 (*c* 3.7, $CHCl_3$); ^{1}H NMR δ 0.85 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 1.15 (s, 3H), 1.22 (m, 2H), 1.23 (s, 3H), 1.31 (d, *J* = 7.1 Hz, 3H), 1.4 (m, 1H), 1.5 (m, 1H), 1.65-1.75 (m, 1H), 2.00 (d, *J* = 10.5 Hz, 1H), 2.51 (s, 3H), 2.68 (m, 1H), 2.97 (dt, *J* = 7.1 Hz, *J* = 6.8 Hz, 1H), 3.31 (d, *J* = 18.1 Hz, 1H), 3.51 (d, *J* = 18.1 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 7.48 (dd, *J* = 7.6 Hz, *J* = 7.8 Hz, 1H), 8.28 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 19.67 (q), 24.12 (q), 24.64 (t), 25.74 (q), 25.95 (q), 29.22 (q), 32.67 (q), 35.03 (t), 42.08 (t), 43.49 (t), 47.34 (s), 50.98 (d), 56.11 (s), 62.93 (s), 120.07 (d), 121.12 (d), 135.49 (d), 161.32 (s), 177.43 (s); HRMS calcd. 317.218 found 317.218. Anal. Calcd. for $C_{20}H_{31}NS$: C, 75.65; H, 9.84; N, 4.41. Found C, 75.60; H, 9.85; N, 4.35.

2-Methyl-6-[[(1*R*,2*R*)-1,3,3-trimethyl-2-(*n*-propylsulfanyl)bicyclo[2.2.1]hept-2-yl]methyl]pyridine (+)-**5.4d.** Preparation of this compound was accomplished according to general procedure B starting from (+)-**3.11f** (1.00 g, 3.63 mmol), sodium hydride (0.17 g, 7.08 mmol) and n-propyl iodide (0.92 g, 5.41 mmol) to afford (+)-**5.4d** after Kugelrohr distillation (0.5 mmHg, 170 °C) as a colorless solid (0.78 g, 2.46 mmol, 68%): mp 42-43 °C; $[\alpha]^{23}_{D}$ +13.8 (*c* 4.0, $CHCl_3$); ^{1}H NMR δ 0.86 (s, 3H), 0.92 (t, *J* = 7.33 Hz, 3H), 1.12 (m, 1H), 1.17 (s, 3H), 1.18 (s, 3H), 1.20 (m, 1H), 1.4-1.55 (m, 4H), 1.7 (m, 1H), 2.00 (d, *J* = 10.3 Hz, 1H), 2.3 (m, 1H), 2.51 (s, 3H), 2.6 (m, 2H), 3.25 (d, *J* = 17.57 Hz, 1H), 3.44 (d, *J* = 17.57 Hz, 1H), 6.94 (d, *J* = 7.3 Hz, 1H), 7.45 (dd, *J* = 7.3 Hz, *J* = 8.1 Hz, 1H), 8.25 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ 13.87 (q), 19.97 (q), 22.45 (t), 24.39 (q), 24.48 (q), 24.78 (t), 29.39 (q), 31.66 (t), 34.76 (t), 41.87 (t), 42.34 (t), 46.93 (s), 51.12 (d), 56.16 (s), 61.72 (s), 120.13 (d), 120.74 (d), 135.89 (d), 156.67 (s), 161.04 (s); HRMS calcd. 317.218, found 317.220. Anal. Calcd. for $C_{20}H_{31}NS$: C, 75.65; H, 9.84; S, 10.10. Found C, 76.02; H, 9.84; S, 10.06;

2-Methyl-6-[[(1*R*,2*R*)-1,3,3-trimethyl-2-(benzylsulfanyl)bicyclo[2.2.1]hept-2-yl]methyl]pyridine (–)-**5.4e.** This compound was prepared according to procedure B starting from (+)-**3.11f** (0.39 g, 1.42 mmol), sodium hydride (0.05 g, 2.1 mmol), and benzyl bromide (0.29 g, 1.7 mmol), to yield a colorless solid (0.42 g, 1.25 mmol, 81%): mp 57-58 °C; $[\alpha]^{23}_{D}$ –28 (*c* 2.2, $CHCl_3$); ^{1}H NMR δ 0.92 (s, 3H), 1.16 (s, 3H), 1.18 (m, 1H), 1.29 (s, 3H), 1.32 (m, 1H), 1.47 (m, 1H), 1.56 (m, 1H), 1.76 (m, 1H), 2.04 (d, *J* = 10.25 Hz, 1H), 2.55 (s, 3H), 2.77 (m, 1H), 3.37 (d, *J* = 17.94 Hz, 1H), 3.51 (d, *J* = 10.25 Hz, 1H), 3.58 (d, *J* = 17.94 Hz, 1H),

3.82 (d, *J* = 10.25 Hz, 1H), 7.00 (d, *J* = 7.33 Hz, 1H), 7.2 (m, 5H), 7.54 (dd, *J* = 7.33 Hz, *J* = 8.06 Hz, 1H), 8.33 (d, *J* = 8.06 Hz, 1H); ^{13}C NMR δ 20.31 (q), 24.26 (q), 24.62 (q), 24.87 (t), 29.41 (q), 34.94 (t), 35.04 (t), 42.08 (t), 42.44 (t), 47.19 (s), 51.24 (d), 56.33 (s), 62.51 (s), 120.40 (d), 120.86 (d), 126.94 (d), 128.27 (d), 128.45 (d), 129.10 (d), 136.09 (d), 137.82 (s), 156.98 (s), 160.86 (s); HRMS calcd. 365.217, found 365.218. Anal. Calcd. for $C_{24}H_{31}NS$: C, 78.85; H, 8.55; N, 3.83. Found C, 78.83; H, 8.73; N, 3.71.

2-Methyl-6-[[(1*S*,2*S*)-1,3,3-trimethyl-2-(benzylsulfanyl)bicyclo[2.2.1]hept-2-yl]methyl]pyridine (+)-**5.4e.** This compound was prepared as described above but starting from (–)-**3.11f**. mp 57-58 °C; $[\alpha]^{23}_{D}$ +30 (*c* 2.0, $CHCl_3$).

2,6-Bis[[(1*R*,2*R*)-1,3,3-trimethyl-2-(methylsulfanyl)bicyclo[2.2.1]hept-2-yl]-methyl]pyridine 5.5a. This material was prepared according to general procedure A starting from **3.1f** (1.0 g, 2.26 mmol), K_2CO_3 (0.48 g, 3.4 mmol), and methyl iodide (0.62 g, 4.5 mmol) to yield **5.5a** as a colorless solid that was recrystallized from hexane (1.0 g, 2.12 mmol, 94%): mp 164-165 °C; $[\alpha]^{23}_{D}$ +33 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 0.87 (s, 6H), 1.14 (s, 6H), 1.18 (s, 6H), 1.20 (m, 4H), 1.42 (m, 2H), 1.53 (d, *J* = 4.39 Hz, 2H), 1.72 (m, 2H), 1.96 (s, 6H), 1.98 (m, 2H), 2.61 (m, 2H), 3.21 (d, *J* = 17.58 Hz, 2H), 3.43 (d, *J* = 17.58 Hz, 2H), 7.50 (t, *J* = 7.86, 1H), 8.13 (d, *J* = 7.86 Hz, 2H); ^{13}C NMR δ 13.57 (q), 20.16 (q), 24.20 (q), 24.75 (t), 29.43 (q), 34.66 (t), 41.34 (t), 41.99 (t), 46.71 (s), 51.10 (d), 56.05 (s), 60.91 (s), 120.77 (d), 135.38 (d), 159.87 (s); HRMS calcd. 471.298, found 471.299. Anal. Calcd. for $C_{29}H_{45}NS_2$: C, 73.83; H, 9.61; N, 2.97. Found C, 73.67; H, 9.61; N, 2.95.

2,6-Bis[[(1*R*,2*R*)-1,3,3-trimethyl-2-(ethylsulfanyl)bicyclo[2.2.1]hept-2-yl]methyl]pyridine 5.5b. For this compound, general procedure B was used, starting from **3.1f** (0.45 g, 1.02 mmol), sodium hydride (0.06 g, 2.50 mmol), and ethyl bromide (0.27 g, 2.48 mmol). Compound **5.5b** was obtained as a colorless solid that was recrystallized from methanol at –20 °C (0.45 g, 0.91 mmol, 89%): mp 38-39 °C; $[\alpha]^{23}_{D}$ +15 (*c* 4.0, $CHCl_3$); ^{1}H NMR δ 0.88 (s, 6H), 1.09 (t, *J* = 7.69 Hz, 6H), 1.16 (s, 6H), 1.18 (s, 6H), 1.20-1.26 (m, 4H), 1.35-1.50 (m, 2H), 1.54 (m, 2H), 1.74 (m, 2H), 2.00 (d, *J* = 9.52 Hz, 2H), 2.29 - 2.37 (m, 2H), 2.56-2.66 (m, 4H), 3.22 (d, *J* = 17.21 Hz, 2H), 3.44 (d, *J* = 17.21 Hz, 2H), 7.52 (t, *J* = 7.69 Hz, 1H), 8.14 (d, *J* = 7.69 Hz, 2H); ^{13}C NMR δ 13.70 (q), 20.09 (q), 23.59 (t), 24.27 (q), 24.80 (t), 29.36 (q), 34.85 (t), 41.86 (t), 42.33 (t), 46.86 (s), 51.13 (d), 56.08 (s), 61.18 (s), 120.94 (d), 135.19 (d), 160.01 (s); HRMS calcd. 499.333, found 499.333. Anal. Calcd. for $C_{31}H_{49}NS_2$: C, 74.49; H, 9.88; N, 2.80. Found C, 72.96; H, 10.05; N, 2.73.

2,6-Bis[[(1*R*,2*R*)-1,3,3-trimethyl-2-(*iso*-propylsulfanyl)bicyclo[2.2.1]hept-2-yl]methyl]pyridine 5.5c. This compound was prepared according to the general procedure B starting from **3.1f** (1.00 g, 2.26 mmol), sodium hydride (0.14 g, 5.83 mmol) and *iso*-propyl bromide (0.69 g, 5.61 mmol). The dithioether was recrystallized from ethanol at – 20 °C yielding **5.5c** as a colorless solid (0.60 g, 1.14 mmol, 50%): mp 82-84 °C; $[\alpha]^{23}_{D}$ +41 (*c* 2.0, $CHCl_3$); ^{1}H NMR δ. 0.86 (s, 6H), 0.97 (d, *J* = 6.59 Hz, 6H), 1.14 (m, 2H), 1.16 (s, 6H), 1.2.3 (m, 2H), 1.25 (s, 6H), 1.30 (d, *J* = 6.59 Hz, 6H), 1.38-1.48 (m, 2H), 1.52-1.54 (m, 2H), 1.67-1.79 (m, 2H), 1.99 (d, *J* = 9.52 Hz, 2H), 2.62 - 2.71 (m, 2H), 2.96 (dt, *J* = 6.59 Hz, *J* = 6.59 Hz, 2H), 3.29 (d, *J* = 18.31 Hz, 2H), 3.51 (d, *J* = 18.31 Hz, 2H), 7.50 (t, *J* = 8.05 Hz, 1H), 8.17 (d, *J* = 8.05 Hz, 2H); ^{13}C NMR δ 19.80 (q), 24.10 (q), 24.65 (t), 25.69 (q), 25.95 (q), 29.12 (q), 32.65 (d), 35.06 (t), 42.08 (t), 43.41 (t), 47.26 (s), 51.02 (d), 56.10 (s), 62.99 (s), 124.84 (d), 134.47 (d), 160.30 (s); HRMS calcd. 527.362, found 527.364. Anal. Calcd. for $C_{33}H_{53}NS_2$: C, 75.08; H, 10.12; N, 2.65 . Found C, 74.97; H, 10.22; N, 2.69.

2,6-Bis[[(1*R*,2*R*)-1,3,3-trimethyl-2-(*n*-propylsulfanyl)bicyclo[2.2.1]hept-2-yl]methyl]pyridine 5.5d. From **3.1f** (0.48 g, 1.08 mmol), sodium hydride (0.07 g, 2.92 mmol), and *n*-propyl iodide (0.46 g, 2.71 mmol), **5.5d** was obtained as a solid that was recrystallized from ethanol at –20 °C (0.36 g, 0.68 mmol, 63%): mp 90-91 °C; $[\alpha]^{23}_{D}$ +24.1 (*c* 4.1, $CHCl_3$); ^{1}H NMR δ 0.89 (s, 6H), 0.91 (t, *J* = 7.32 Hz, 6H), 1.17 (s, 6H), 1.19 (s, 6H), 1.2-1.3 (m, 6H), 1.4-1.6 (m, 8H), 1.7-1.8 (m, 2H), 2.00 (d, *J* = 9.88 Hz, 2H), 2.2 - 2.3 (m, 2H), 2.5-2.7 (m, 4H), 3.23 (d, *J* = 17.58 Hz, 2H), 3.44 (d, *J* = 17.58 Hz, 2H), 7.51 (t, *J* = 7.69 Hz, 1H), 8.15 (d, *J* = 7.69 Hz, 2H); ^{13}C NMR δ 13.68 (q), 20.07 (q), 23.57 (t), 24.25 (q), 24.77 (t), 29.35 (q), 34.83 (t), 41.82 (t), 42.31 (t), 46.83 (s), 51.10 (d), 56.05 (s), 62.15 (s), 120.91 (d), 135.15 (d), 160.00 (s); HRMS calcd. 527.362, found 527.361. Anal. Calcd. for $C_{33}H_{53}NS_2$: C, 75.08; H, 10.12; N, 2.65 . Found C, 75.02; H, 10.16; N, 2.70.

2,6-Bis[[(1*R*,2*R*)-1,3,3-trimethyl-2-(benzylsulfanyl)bicyclo[2.2.1]hept-2-yl]methyl]pyridine 5.5e. From **3.1f** (0.50 g, 1.13 mmol), sodium hydride (0.11 g, 4.58 mmol), and benzyl bromide (0.58 g, 3.39 mmol), **5.5e** was obtained as a colorless solid that was recrystallized from dichloromethane/ethanol (0.56 g, 0.90 mmol, 80%): mp 135-136 °C; $[\alpha]^{23}_{D}$ –100 (*c* 2.6, $CHCl_3$); ^{1}H NMR δ 0.97 (s, 6H), 1.19 (s, 6H), 1.22 (s, 6H), 1.25 (m, 2H), 1.30 (s, 6H), 1.47 (m, 2H), 1.58 (m, 2H), 1.77 (m, 2H), 2.04 (d, *J* = 9.52 Hz, 2H), 2.78 (m, 2H), 3.38 (d, *J* = 16.86 Hz, 2H), 3.51 (d, *J* = 10.62 Hz, 2H), 3.61 (d, *J* = 16.86 Hz, 2H), 3.83 (d, *J* = 10.62 Hz, 2H), 7.1 (m, 10H), 7.61 (t, *J* = 7.69 Hz, 1H), 8.29 (d, *J* = 7.69 Hz, 2H); ^{13}C NMR δ 20.35 (q), 24.19 (q), 24.82 (t), 29.38 (q), 34.93 (t), 35.01 (t), 42.02 (t), 42.41 (t), 47.10 (s), 51.16 (d), 56.21 (s), 62.94 (s), 121.24 (d), 126.84 (d), 128.34 (d), 129.02(d), 135.38 (d), 137.78 (s), 160.01 (s), 177.42 (s); HRMS calcd. 623.362, no proper HRMS could be

obtained, CI(NH_3) gave a molecular ion at *m/e* 624. Anal. Calcd. for $C_{41}H_{53}NS_2$: C, 78.92; H, 8.56; S, 10.28. Found C, 78.75; H, 8.63; S, 10.25.

Palladium-Allyl Complex of (+)-**5.4c. (5.6).** A solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.10 g, 0.27 mmol) and (+)-**5.4c** (0.20 g, 0.63 mmol) in dichloromethane (10 mL) was stirred for 1 h and treated with $AgPF_6$ (0.16 g, 0.63 mmol) in 10 mL of THF. Stirring continued for 10 min, and the mixture was filtered over celite. The solution was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the solid was recrystallized from hexane/dichloromethane by slow evaporation of the solvent, yielding **5.6** as colorless crystals (0.24 g, 0.52 mmol, 94%): **5.6** isomerized upon dissolution. ^{1}H NMR of **5.6a**: δ 0.83 (t, *J* = 7.32 Hz, 3H), 1.17 (s, 3H), 1.26 (m, 1H), 1.27 (s, 3H), 1.38 (m, 2H), 1.46 (m, 1H), 1.57 (s, 3H), 1.64 (m, 2H), 1.81 (m, 1H), 1.92 (m, 1H), 2.08 (m, 1H), 2.17 (m, 1H), 2.35 (m, 1H), 2.64 (s, 3H), 2.94 (d, *J* = 12.21 Hz, 1H), 3.58 (d, *J* = 13.67 Hz, 1H), 3.64 (d, *J* = 12.20 Hz, 1H), 3.76 (d, *J* = 12.20 Hz, 1H), 4.33 (d, *J* = 6.35 Hz, 1H), 4.88 (d, *J* = 5.38 Hz, 1H), 5.89 (m, 1H), 7.38 (d, *J* = 7.81 Hz, 1H), 7.65 (d, *J* = 7.81 Hz, 1H), 7.84 (dd, *J* = 7.81 Hz, *J* = 7.81 Hz, 1H). ^{1}H NMR of **5.6b**: δ 0.90 (t, *J* = 7.32 Hz, 3H), 1.18 (s, 3H), 1.26 (m, 1H), 1.30 (s, 3H), 1.38 (m, 2H), 1.41 (s, 3H), 1.46 (m, 1H), 1.62 (m, 2H), 1.64 (m, 2H), 1.75 (m, 1H), 1.92 (m, 1H), 2.08 (m, 2H), 2.17 (m, 1H), 2.80 (s, 3H), 3.39 (d, *J* = 13.18 Hz, 1H), 3.40 (d, *J* = 14.16 Hz, 1H), 3.47 (d, *J* = 14.16 Hz, 1H), 4.33 (d, *J* = 6.35 Hz, 1H), 4.67 (d, *J* = 6.84 Hz, 1H), 5.70 (m, 1H), 7.41 (d, *J* = 7.32 Hz, 1H), 7.59 (d, *J* = 7.82 Hz, 1H), 7.84 (dd, *J* = 7.32 Hz, *J* = 7.82 Hz, 1H).

Crystal Structure of 5.6

Crystal Data : Formula: $[C_{23}H_{36}NPdS]^+[PF_6]^-$, M = 400.29, colorless transparent crystals of approximate dimensions of 0.42 x 0.52 x 0.088 mm, orthorhombic, $P2_12_12_1$, a = 10.732(1), b = 14.816(1), c = 16.179(1) Å, V= 2572.5(3) $Å^3$; Z= 4, D_x = 1.575 g cm^{-3}, μ = 9.2 cm^{-1}, F(000) = 1248. *Data collection*: The data were collected on an Enraf-Nonius CAD-4F diffractometer (Mo tube, 50 kV, 40 mA, monochromated Mo-Kα radiation (λ = 0.71073 Å), Δω = 0.80 + 0.34 tg θ; T = 130 K; θ range 1.26°-26.5°, reflections collected: 6071 independent reflections 5335. *Solution and refinement*: The structure was solved by Patterson methods and extension of the model was accomplished by direct methods applied to difference structure factors using the program DIRDIF. Refined anisotropically by full-matrix least squares based on F^2 (SHELXL-93); data/parameters 5335/340; R_f = 0.0509 [$F_o > 4.0\ \sigma(F_o)$], wR_f = 0. 1 223 [$F^2 > 0$]; absolute-structure parameters; maximal residual electron density 1.96(7) e/$Å^3$. The program PLUTO has been used for graphical representation of the crystal structure.

Table 5.4 : *Interatomic distances and selected bond angles for compound **5.6***

Bond distances (Å)					
Pd	-S	2.3588(15)[b]	C(1)	-C(2)	1.448(14)
Pd	-N	2.112(5)	C(2)	-C(3)	1.304(15)
Pd	-C(1)[a]	2.120(7)	C(8)	-C(10)	1.498(8)
Pd	-C(2)	2.110(9)	C(10)	-C(11)	1.573(6)
Pd	-C(3)	2.195(10)	H(1)	-C(1)	0.9504
S	-C(11)	1.859(5)	H(1')	-C(1)	0.9502
S	-C(21)	1.821(5)	H(2)	-C(2)	0.9500
N	-C(4)	1.365(8)	H(3)	-C(3)	0.9495
N	-C(8)	1.338(8)	H(3')	-C(3)	0.9500

Bond angles (deg.)							
S	-Pd	-N	87.12(14)	Pd	-C(2)	-C(3)	76.0(6)
S	-Pd	-C(1)	102.2(3)	C(1)	-C(2)	-C(3)	121.5(10)
S	-Pd	-C(2)	136.9(3)	Pd	-C(3)	-C(2)	68.9(6)
S	-Pd	-C(3)	169.5(3)	N	-C(4)	-C(5)	121.0(6)
N	-Pd	-C(1)	169.0(3)	N	-C(4)	-C(9)	117.4(7)
N	-Pd	-C(2)	133.4(3)	C(7)	-C(8)	-C(10)	120.5(5)
N	-Pd	-C(3)	102.8(3)	C(8)	-C(10)	-C(11)	120.0(4)
C(1)	-Pd	-C(2)	40.0(4)	S	-C(11)	-C(10)	109.5(3)
C(1)	-Pd	-C(3)	67.6(4)	S	-C(11)	-C(12)	107.5(3)
C(2)	-Pd	-C(3)	35.2(4)	S	-C(11)	-C(16)	112.8(3)
Pd	-S	-C(11)	101.52(16)	C(10)	-C(11)	-C(12)	109.5(4)
Pd	-S	-C(21)	100.71(17)	C(10)	-C(11)	-C(16)	114.6(4)
C(11)	-S	-C(21)	110.0(2)	C(12)	-C(11)	-C(16)	102.4(4)
Pd	-N	-C(4)	123.5(5)	H(1)	-C(1)	-Pd	75.54
Pd	-N	-C(8)	117.1(4)	H(1')	-C(1)	-Pd	126.76
C(4)	-N	-C(8)	119.4(6)	H(2)	-C(2)	-Pd	126.44
Pd	-C(1)	-C(2)	69.6(5)	H(3)	-C(3)	-Pd	74.12
Pd	-C(2)	-C(1)	70.3(5)	H(3')	-C(3)	-Pd	129.23

[a] The numbering for the crystal data does not follow the numbering used in nomenclature.

[b] Standard deviation in parentheses.

(1*R*,2*R*)-1,3,3-trimethyl-2-(2-pyridinylmethyl)bicyclo[2.2.1]heptane-2-thiol 5.8. To a solution of 2-methylpyridine (3.20 g, 34.4 mmol) in 150 mL of THF at –70 °C was added *n*-butyllithium (1.6 M in hexane, 21 mL, 33.6 mmol). The mixture was stirred for 30 min at –40 °C and cooled to –70 °C again. A solution of R-thiofenchone (4.70 g, 27.9 mmol) in 15 mL

of THF was added and the mixture allowed to reach ambient temperature in 3 h. To the mixture was added 15 mL of 5 N HCl. Stirring was continued for 15 min and the solution subsequently neutralized with 2 N NaOH. The mixture was extracted three times with dichloromethane, and the combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by means of column chromatography (silica gel, hexane/diethyl ether 9:1) and recrystallization from hexane to yield **5.8** as colorless needles (7.11 g, 27.2 mmol, 81%): mp 96-97 °C; $[\alpha]^{23}_D$ +109 (*c* 2.8, CH_2Cl_2); ^{1}H NMR δ 0.80 (s, 3H), 1.15 (m, 2H), 1.19 (s, 3H), 1.24 (s, 3H), 1.4 (m, 1H), 1.65 (m, 1H), 1.76 (m, 1H), 1.95 (d, *J* = 10.25 Hz, 1H), 2.20 (m, 1H), 3.34 (s, 2H), 4.30 (s, SH), 7.08 (dd, *J* = 5.12 Hz, *J* = 6.95 Hz, 1H), 7.31 (d, *J* = 8.06 Hz, 1H), 7.54 (dd, *J* = 8.06 Hz, *J* = 6.95 Hz, 1H), 8.49 (d, *J* = 5.12 Hz, 1H); ^{13}C NMR δ 18.31 (q), 24.56 (t), 27.28 (q), 28.97 (q), 33.77 (t), 40.42 (t), 45.63 (s), 48.23 (t), 50.95 (d), 54.58 (s), 120.62 (d), 124.73 (d), 135.74 (d), 147.57 (d), 161.92 (s); HRMS calcd. 261.156 found 261.155. Anal. Calcd. for $C_{16}H_{23}NS$: C, 73.51; H, 8.87; N, 5.36. Found C, 73.73; H, 8.88; N, 5.41.

2-[[(1*R*,2*R*)-1,3,3-trimethyl-2-(benzylsulfanyl)bicyclo[2.2.1]hept-2-yl]methyl]pyridine 5.9. This compound was prepared from **5.8** (0.75g, 2.87 mmol), sodium hydride (0.10g, 4.3 mmol), and benzyl bromide (0.51, 2.98 mmol) according to general procedure B. The product was recrystallized from hexane at –20 °C to afford **5.9** as a colorless solid (0.60g, 1.72 mmol, 60%): mp 104-105 °C; $[\alpha]^{23}_D$ –43 (*c* 3.5, $CHCl_3$); ^{1}H NMR δ 0.91 (s, 3H), 1.16 (s, 3H), 1.23 (m, 2H), 1.28 (s, 3H), 1.48 (m, 1H), 1.58 (d, *J* = 4.39 Hz, 1H), 1.77 (m, 1H), 2.02 (d, *J* = 9.52 Hz, 1H), 2.75 (m, 1H), 3.42 (d, *J* = 17.57 Hz, 1H), 3.53 (d, *J* = 10.25 Hz, 1H), 3.6 (d, *J* = 17.57 Hz, 1H), 3.82 (d, *J* = 10.25 Hz, 1H), 7.2 (m, 5H), 7.64 (dd, *J* = 7.69 Hz, *J* = 8.06 Hz, 1H), 8.47 (d, *J* = 8.06 Hz, 1H), 8.53 (d, *J* = 4.03 Hz); ^{13}C NMR δ 20.24 (q), 24.07 (q), 24.80 (t), 29.36 (q), 34.75 (t), 34.88 (t), 42.07 (s), 42.39 (t), 47.18 (s), 51.02 (d), 56.09 (s), 120.86 (d), 123.95 (d), 126.85 (d), 128.34 (d), 128.94 (d), 135.72 (d), 137.58 (s), 148.47 (d), 161.39 (s); HRMS calcd. 351.202 found no proper HRMS could be obtained, CI(NH_3) gave a molecular ion at *m/e* 352. Anal. Calcd. for $C_{23}H_{29}NS$: C, 78.58; H, 8.31; N, 3.98. Found C, 78.29; H, 8.33; N, 3.98.

Palladium-Chloride Complex of 5.5e.

A solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (37 mg, 0.10 mmol) and **5.5e** (0.10 g, 0.16 mmol) in dichloromethane (10 mL) was stirred for 1 h and treated with $AgBF_4$ (39 mg, 0.20 mmol) in 10 mL of THF. Stirring continued for 30 min, and the mixture was filtered over Celite. The solution was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the

complex was obtained as a yellow solid that was recrystallized from dichloromethane by isothermal distillation of hexane into the solution. Compound **5.10** was obtained as yellow crystals suitable for X-ray (0.12 g, 0.14 mmol, 88%): ^{1}H NMR δ 0.68 (s, 6H), 1.28 (s, 6H), 1.38 (d, *J* = 10.42 Hz, 2H), 1.44 (s, 6H), 1.46 (m, 2H), 1.62 (m, 2H), 1.74 (d, *J* = 3.74 Hz, 2H), 1.95 (m, 4H), 2.19 (d, *J* = 11.2 Hz, 2H), 2.46 (d, *J* = 13.2 Hz, 2H), 3.32 (d, *J* = 14.6 Hz, 2H), 3.71 (d, *J* = 13.2 Hz, 2H), 3.74 (d, *J* = 14.6 Hz, 2H), 7.16 (d, *J* = 7.47 Hz, 4H), 7.33 (t, *J* = 7.62 Hz, 2H), 7.42 (dd, *J* = 7.62 Hz, *J* = 7.47 Hz, 4H), 8.12 (d, *J* = 7.77 Hz 2H), 8.34 (t, *J* = 7.77 Hz, 1H),

Crystal Structure of 5.10:

Crystal data: Formula: $[C_{41}H_{53}ClNPdS_2]^+.[BF_4]^-$, M = 852.69, crystal of approximate dimensions of 0.25 x 0.25 x 0.25 mm. ('spherical polyhedron'), orthorhombic, $P2_12_12_1$, a = 15.279(1), b = 15.351(1), c = 16.423(1) Å, V = 3852.0(4) Å^3 Z = 4, D_x = 1.470 g cm^{-3}, λ(MoKα) = 0.71073 Å, μ = 7.1 cm^{-1}, F(000) = 1768, T = 130 K, $wR(F^2)$ = 0.1047 for 8385 reflections with $F_o^2 \geq 0$ and 656 parameters and $R(F)$ = 0.0419 for 7079 reflections obeying $F_o \geq 4.0\ \sigma(F_o)$ criterion of observability. Enraf-Nonius *CAD-4F* diffractometer, interfaced to a *INDY* (*Silicon Graphics*) *UNIX* computer (Mo tube, 50 kV, 40 mA, monochromated Mo-Kα radiation, Δω = 0.90 + 0.34 tg θ). *Solution and refinement*: The structure was solved by Patterson methods and extension of the model was accomplished by direct methods applied to difference structure factors using the program DIRDIF. Refined anisotropically by full-matrix least squares based on F^2 (SHELXL-93); absolute-structure parameters; maximal residual electron density 0.72(8) e/Å^3. The program PLUTO has been used for graphical representation of the crystal structure.

Table 5.5 : *Interatomic distances and selected bond angles for compound **5.10***

Interatomic Distances (Å)					
Pd(1)[a]	-Cl(1)	2.2850(12)[b]	S(2)	-C(35)	1.835(5)
Pd(1)	-S(1)	2.3138(12)	N(1)	-C(1)	1.349(6)
Pd(1)	-S(2)	2.3106(11)	N(1)	-C(5)	1.347(6)
Pd(1)	-N(1)	2.006(3)	C(1)	-C(24)	1.510(7)
S(1)	-C(7)	1.861(5)	C(5)	-C(6)	1.513(7)
S(1)	-C(17)	1.833(5)	C(6)	-C(7)	1.539(7)
S(2)	-C(25)	1.852(5)	C(24)	-C(25)	1.562(7)

Bond angles (deg.)							
Cl(1)	-Pd(1)	-S(1)	93.29(4)	C(2)	-C(1)	-C(24)	121.8(4)
Cl(1)	-Pd(1)	-S(2)	90.19(4)	N(1)	-C(5)	-C(4)	120.1(4)
Cl(1)	-Pd(1)	-N(1)	175.9(1)	N(1)	-C(5)	-C(6)	117.9(4)
S(1)	-Pd(1)	-S(2)	175.95(4)	C(4)	-C(5)	-C(6)	121.9(4)
S(1)	-Pd(1)	-N(1)	88.18(10)	C(5)	-C(6)	-C(7)	120.4(4)
S(2)	-Pd(1)	-N(1)	88.49(10)	S(1)	-C(7)	-C(6)	109.3(3)
Pd(1)	-S(1)	-C(7)	101.84(16)	S(1)	-C(7)	-C(8)	106.9(3)
Pd(1)	-S(1)	-C(17)	104.09(16)	S(1)	-C(7)	-C(12)	113.2(3)
C(7)	-S(1)	-C(17)	106.2(2)	C(6)	-C(7)	-C(8)	111.9(4)
Pd(1)	-S(2)	-C(25)	102.67(16)	C(6)	-C(7)	-C(12)	113.8(4)
Pd(1)	-S(2)	-C(35)	102.87(16)	C(1)	-C(24)	-C(25)	120.9(4)
C(25)	-S(2)	-C(35)	106.4(2)	S(2)	-C(25)	-C(24)	108.7(3)
Pd(1)	-N(1)	-C(1)	119.9(3)	S(2)	-C(25)	-C(26)	108.4(3)
Pd(1)	-N(1)	-C(5)	118.5(3)	S(2)	-C(25)	-C(30)	113.5(3)
C(1)	-N(1)	-C(5)	121.5(4)	C(24)	-C(25)	-C(26)	110.4(4)
N(1)	-C(1)	-C(2)	120.4(4)	C(24)	-C(25)	-C(30)	113.2(4)
N(1)	-C(1)	-C(24)	117.5(4)				

[a] The numbering for the crystal data does not follow the numbering used in nomenclature.

[b] Standard deviation in parentheses.

5.7 References.

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CHAPTER 6

Catalysis with Pyridine Alcohols and Thiols.*

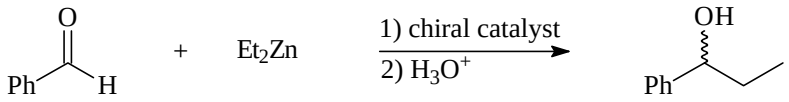
Abstract: A combinatorial approach for the diethylzinc addition to four different aldehydes was used to test the pyridine alcohols and thiols described in Chapter 2 and 3 as chiral catalyst in enantioselective reactions. Moderate to high enantiomeric excesses were obtained. The enantiomeric composition of the reaction mixture was analyzed by means of chiral GC. Best results were obtained with *cis*-**2.3g** as ligand. A pure heuristic explanation for the results was used to devise a possible mechanism with its intermediates **6.15**. With these postulated intermediate structures it was also possible to explain the inactivity of the *trans*-**2.3g** ligand. The pyridine diols **2.1e** and *cis*-*cis*-**2.1g** were found to be completely inactive whereas the dithiol **3.1f** was found to give the alcohols only in very low yield. A tightly bound zinc ion in the cavity of the ligands is thought to be the reason for this.

A dibenzyl zirconium compound **6.17** of pyridine diol *cis*-*cis*-**2.1g** was synthesized. The ligand binds in a meridional fashion to the metal center, inducing a C_2-symmetric geometry. Reaction of the dibenzyl zirconium complex **6.17** with tris(pentafluorophenyl)-borane resulted in the formation of a cationic benzyl species **6.18**. In d_8-toluene, the electron deficient metal center is stabilized by coordination of the benzyl borate anion. In d_5-bromobenzene, a solvent separated ion-pair **6.18b** is formed in which the remaining benzyl ligand is η^2-coordinated to the metal center. Treatment of the dibenzyl zirconium compound with trityl tetrakis(pentafluorophenyl)borate results in the formation of a similar solvent separated ion pair **6.19**. Both the solvent separated and the contact ion-pair are active in the polymerization of α-olefins; resulting in the formation of fully atactic polyolefins (Activity: 0.9 $kg \cdot mol^{-1} \cdot h^{-1}$ for **6.19** in the polymerization of propene).

6.1 Asymmetric 1,2-Addition of Diethylzinc to Aldehydes.

6.1.1 Introduction.

One of the most intensively studied catalytic asymmetric transformation in organic chemistry is the 1,2-addition of dialkylzinc reagents to aldehydes like benzaldehyde **6.1a**. Several catalysts have been found to give high enantioselection (>98%) in the formation of the addition product **6.2a** (Scheme 6.1).

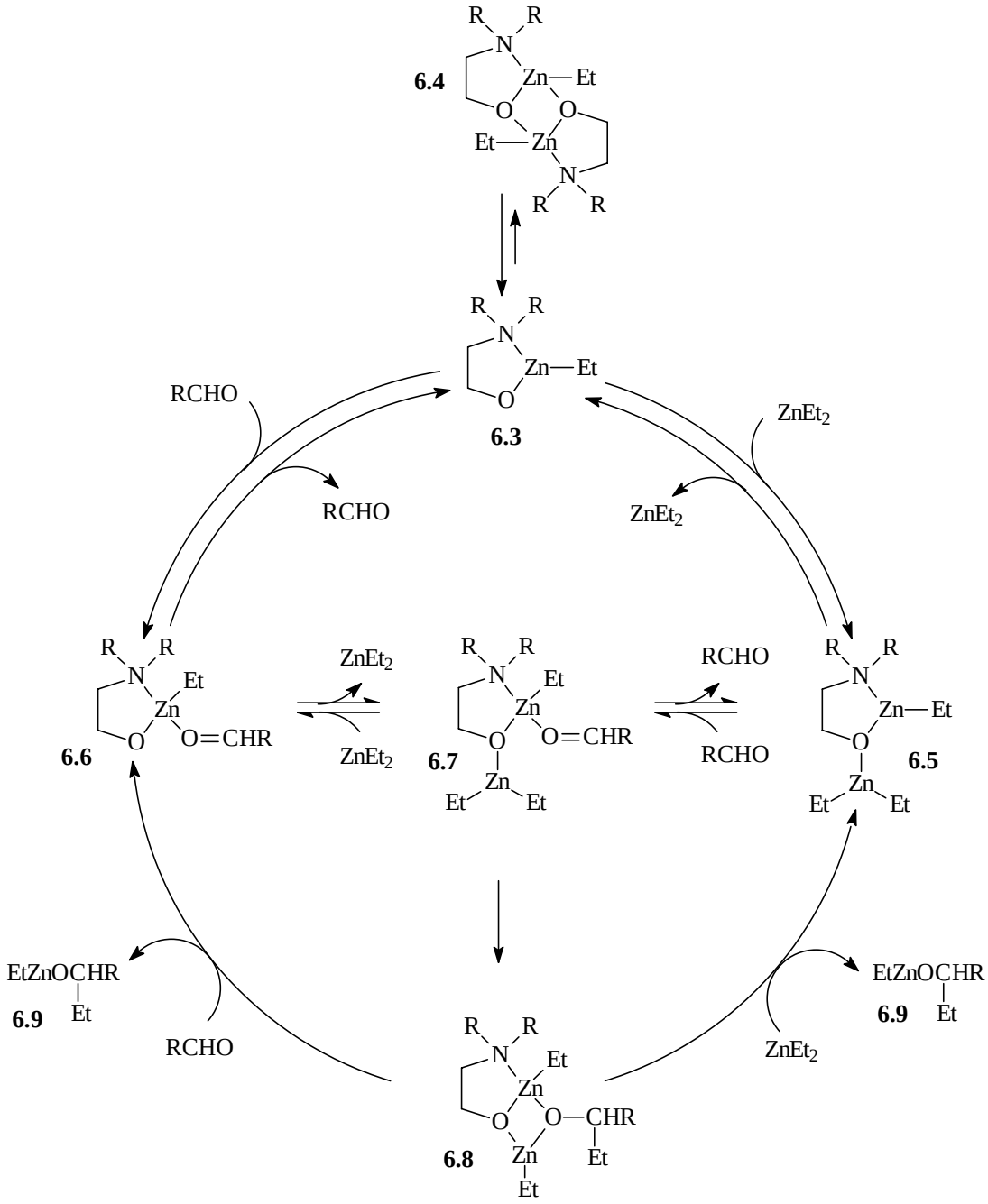


6.1a **6.2a**

Scheme 6.1 *Asymmetric 1,2-addition of diethylzinc to aldehydes.*

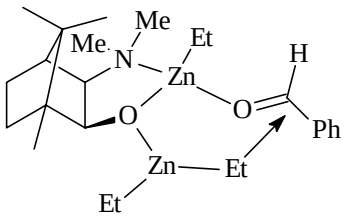
Although the product of this type of reaction is of little practical interest, this well documented reaction today has become a standard test reaction to study the catalytic properties of newly prepared ligands. The reaction of Scheme 6.1 is easy to perform, reproducible and in absence of the catalyst the reaction proceeds sluggishly and often reduction of the aldehyde to the alcohol is observed.[1] Many types of ligands such as diamines,[2] titanium alkoxides,[3] chinchona alkaloids,[4] polymer bound β-amino alcohols,[5] proline derivatives,[6] TADDOLs,[7] bipyridines,[8] and ephedrine derivatives[9] catalyze this reaction. Amino alcohols are the most often used and best studied ligands.[10] The analogous amino thiols have been a subject of study in our group.[11]

The mechanism of the addition of diethylzinc to aldehydes for the use of amino alcohols as ligand is well known because of the work of Soai[12] and Noyori[13] (Scheme 6.2). In a first step the diethylzinc reacts with an amino alcohol to form a monomeric zinc alkoxide **6.3,** which is in equilibrium with the dimeric alkoxide **6.4**. The dimeric alkoxide **6.4** is inactive and dissociates easily to the active monomeric zinc alkoxide **6.3**. This alkoxide subsequently forms the monoalkoxide diethylzinc complex **6.5** upon reaction with another equivalent of diethylzinc or the monoalkoxide-aldehyde complex **6.6**. Addition of the aldehyde to **6.5** leads to the formation of intermediate **6.7**, which can also be formed from **6.6** by addition of an equivalent of diethylzinc. Attack of the aldehyde at the carbonyl carbon in intermediate **6.7** yields the alkoxide **6.8**, which is converted back to the complex **6.5** or **6.6** upon addition of diethylzinc or aldehyde, respectively. The zinc alkoxide **6.9** is split off during this conversion. Workup of this alkoxide **6.9** affords the alcohol **6.2**.

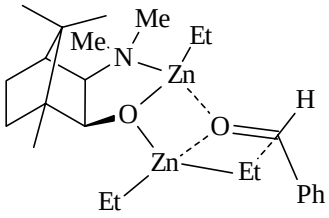


Scheme 6.2 *Proposed mechanism for the diethylzinc addition to aldehydes.*

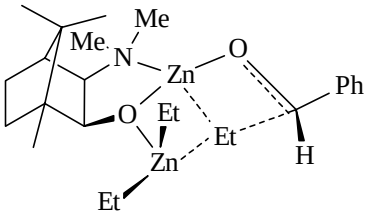
Intensive research on the intermediate **6.7** let to various proposed structures. Evans and Corey postulated **6.7a** as an intermediate in which a six membered transition structure is adapted.[14,9a] Itsuno and Fréchet proposed a μ-O transition structure **6.7b** in which the aldehyde is bridged between two zinc ions.[5] Noyori proposed a μ-R transition structure **6.7c**, which involves bridging of alkyl groups.[15]



6.7a

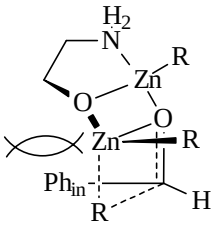


6.7b

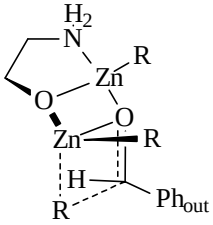


6.7c

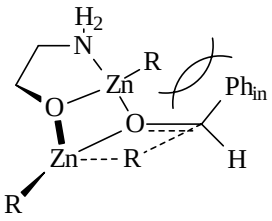
Theoretical studies have been carried out by Noyori using MP2/HF ab initio methods to compute the transition structures with 2-aminoethanol as ligand in a model reaction between $ZnMe_2$ and formaldehyde. Two low energy μ-O transition structures, *syn* and *anti*, were located, but no μ-R structures as proposed before were found.[16] Similar results were found in PM3 calculations for more complicated β-amino alcohols.[17] For the use of chiral β-amino alcohols four possible transition structures **6.10** were found. The Ph_{in} geometries of μ-O transition structures were highly disfavored both for *syn* and *anti* structures due to strong steric repulsions. These unfavorable interactions arise for *syn* structures from the close distances between the Ph_{in} groups and the zinc chelate ring and for the *anti* structures from the close distances between the Ph_{in} groups and the alkyl groups (R) attached to zinc.



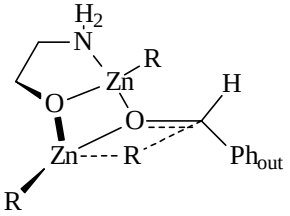
Ph_{in} **6.10**-*syn*



Ph_{out} **6.10**-*syn*

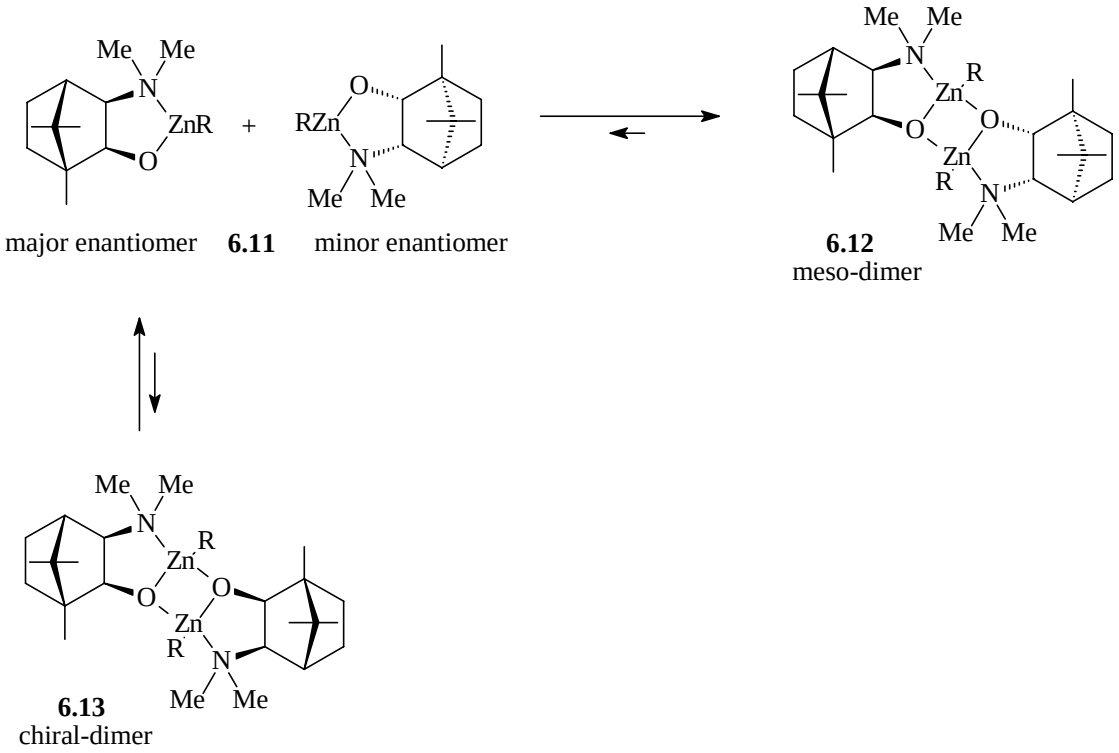


Ph_{in} **6.10**-*anti*



Ph_{out} **6.10**-*anti*

A remarkable non-linear correlation between the enantiomeric excess of the catalyst and the product was observed by Noyori.[15] With optically pure (-)-3-*exo*-(dimethylamino)iosborneol (DAIB) as chiral ligand the formation of 6.2a proceeded in an ee of 99%. However, using the catalyst in an ee of only 15% the product 6.2 is obtained in an ee of 95%. The reason for this behavior can be found in the formation of a stable *meso*-dimer **6.12** between the minor and major monoalkoxides **6.11** of DIAB (Scheme 6.3). The *meso*-dimer **6.12** is relatively stable and does not catalyze the reaction. The major isomer at the same time forms a chiral dimer **6.13**, which easily dissociates to the reactive monomer **6.11**. The relative stability of the *meso*-dimer **6.12** enhances the enantiomeric purity of the actual catalyst and so enhances the enantioselectivity in the formation of the product **6.2a**. Similar non-linear effects in the diethylzinc addition to aldehydes were also found by others.[18]

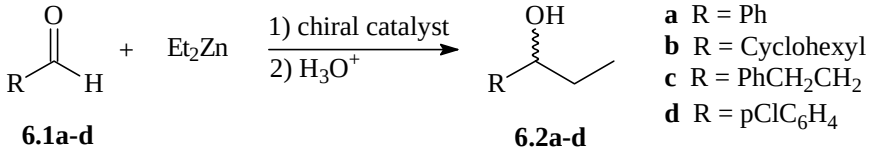


Scheme 6.3 *Non-linear effects in the enantioselective diethylzinc addition*

6.1.2 Combinatorial Approach.

Thus far many compounds have been tested as ligands in the enantioselective addition of diethylzinc to aldehydes and it was of obvious interest to test our pyridine alcohols and thiols in this reaction as well in order to gain information in the transfer of chirality of the ligand onto the substrate. In chapter 5 it was shown that in the palladium catalyzed allylic substitution the enantiomeric outcome was greatly affected by small changes in the ligand as was predicted based on the proposed intermediates.[19] With insight into the well studied mechanism for the diethylzinc addition important features of substituents of the pyridine alcohols and thiols can be examined.

However, testing the selectivities of chiral catalysts in the conversion of various substrates is a time-consuming work. Therefore Gennari[20] and Liskamp[21] introduced a method for testing ligands on a library of substrates. A library of four aldehydes was added to a catalyst in the presence of diethylzinc (Scheme 6.4). After workup of the reaction mixture the products mixture was subjected to chiral GC and the conversions and enantioselectivities of the individual alcohols were determined. Using this method only ¼ of the number of single substrate reactions has to be carried out and information on substituents and their effects on the enantioselection can be obtained quickly.



6.1a-d **6.2a-d**

Scheme 6.4 *Combinatorial approach for the diethylzinc addition.*

6.1.3 Results with Pyridine Alcohols and Thiols.

Our pyridine alcohols and thiols exhibit the same functional groups as the amino alcohols and thiols: a nitrogen for complexation of the zinc (although embedded in a pyridine ring) and an alcohol or thiol function which can form a bond with the zinc atom. Therefore these ligands were expected to behave analogously to the amino alcohols already known. Application of these ligands in the combinatorial approach of the diethylzinc addition to a mixture of aldehydes indeed afforded the corresponding alcohols (Table 6.1). When camphor based pyridine alcohol **2.3e** was used as ligand the alcohols **6.2** were obtained in moderate to good ee. The products were all formed as the R-enantiomer.[22] The best selectivities were found for the aldehydes **6.1a**, **6.1b** and **6.1d** with the phenyl or cyclohexyl group directly adjacent to de aldehyde functionality. It seems that steric bulk is important for the selectivity and a drop in the ee is expected when this bulk is linked with a (CH_2CH_2) spacer. When the pyridine alcohol **2.11e**, which lacks the methyl group on the pyridine ring, was used as ligand the same configuration of the alcohols **6.2** was observed, but the enantiomeric excesses were much lower than for ligand **2.3e**. This observation is in accordance to the results found for the pyridine sulfides in the palladium catalyzed allylic substitution (see Chapter 5). Again the methyl group seems to have a great influence on the enantiomeric outcome of the reaction.

Table 6.1 *Test results with pyridine alcohols.*

Ligand	Enantiomeric excess of alcohols **6.2** (configuration)			
	6.2a	**6.2b**	**6.2c**	**6.2d**
2.3e	76 (R)	76 (R)	46 (R)	75 (R)
2.11e	37 (R)	17 (R)	31 (R)	22 (R)
2.3f (*exo*/*endo*)	74 (S)	63 (S)	32 (S)	65 (S)
2.11f (*exo*/*endo*)	41(S)	23(S)	34(S)	26(S)
2.11f (*exo*)	45 (S)	20 (S)	36 (S)	20 (S)
2.3g (*cis*)	87 (S)	58 (S)	44 (S)	62 (S)
2.3g (*trans*)	l.c.[a]	l.c.	l.c.	l.c.
2.3g (*cis*/*trans*)	83 (S)	56 (S)	41 (S)	58 (S)

a) l.c. = low conversion

The fenchone based pyridine alcohol **2.3f** was synthesized as a mixture of *exo* and *endo*-isomers (1:1), which could not be separated (see Chapter 2). Application of this mixture of isomers in the catalytic reaction afforded the alcohols **6.2** as the S-enantiomer in good enantiomeric excesses. Although this mixture was used as a mixture of isomers there still is a preference for the formation of one of the enantiomers of the products. When the pyridine alcohol **2.11f** was used as a mixture of isomers (*endo*/*exo* = 2:3) the same configuration of the products was obtained and lower enantioselection was observed. The use of the purified *exo*-**2.11f** in the catalytic reaction gave rise to nearly the same results as for the mixture of the enantiomers. From this can be concluded that the *endo*-isomer hardly influences the reaction probably because it has a mismatched configuration. The same phenomenon was found when both isomers of the menthone base pyridine alcohol **2.3g** were used. The *cis*-isomer led to a high enantiomeric excess of the alcohols **6.2** whereas *trans*-**2.3g** hardly gave any product at all. A mixture of both isomers in turn gave comparable results as the *cis*-isomer. For this system the *trans*-isomer is an extreme mismatched isomer that does not lead to a catalytic reaction at all.

When pyridine thiol **3.11f** was applied in the combinatorial catalytic reaction the products were found in a low enantiomeric excess with best results for benzaldehyde. The products all were formed as the S-enantiomer. When the pyridine thiol **5.8**, which lacks the methyl group, the products were formed as the R-enantiomer. As was seen in this reaction before for the camphor based pyridine alcohols **2.3e** and **2.11e** the methyl group has a large influence on the enantiomeric outcome. In the case of the pyridine thiols lack of the methyl group gives rise to the other enantiomer and also to an increase in the enantioselectivity. The pyridine sulfides **5.4** ((-)-**5.4e** shown as an example) did not give any conversion in the catalytic reaction. This is not surprising as these ligands lack the necessary thiol/alcohol functionality to activate the zinc.

Table 6.2 *Test results with pyridine thiols.*

Ligand	Enantiomeric excess of alcohols **6.2** (configuration)			
	6.2a	**6.2b**	**6.2c**	**6.2d**
3.11f	35 (S)	19 (S)	12 (S)	15 (S)
5.8	47 (R)	57 (R)	31 (R)	31 (R)
(-)-**5.4e**	-	-	-	-

When pyridine diols **2.1e** and *cis*-*cis*-**2.1g** were used in the catalyzed reaction no conversion was observed. The diethylzinc probably deprotonated both alcohol functionalities and forms a stable zinc-complex that is not catalytically active. When pyridine dithiol **3.1f** was used as ligand the products were found with only low conversion (3-5%) and with a low ee. Here again the diethylzinc deprotonates the thiol groups and forms a stable zinc complex.

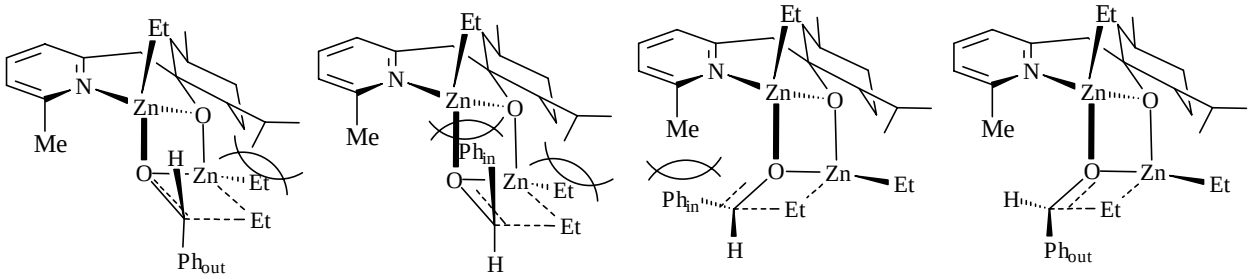
Activation of the diol or dithiol ligands by the addition of TMEDA, as nitrogen activator, as described by Mikami, did not lead to any improvement of the conversions.[23] The addition of a diamine does not lead to the formation of an active catalyst probably because the zinc is too firmly embedded in the ligand.

Table 6.3 *Test results with pyridine diols and dithiols.*

Ligand	Enantiomeric excess of alcohols **6.2** (configuration)			
	6.2a	**6.2b**	**6.2c**	**6.2d**
2.1e	-	-	-	-
cis-*cis*-**2.1g**	-	-	-	-
3.1f	22 (S)	3 (R)	10 (R)	8 (R)

6.1.4 Proposed Intermediate.

The best results were obtained with the menthyl pyridine alcohol *cis*-**2.3g**. We have made attempts to explain this induction of the chirality using the methyl derivative *cis*-**2.3g** based on other proposed *anti* and *syn* transition structures in literature.[16,17] No efforts were made to gain mechanistic evidence on the basis of possible intermediates. A pure heuristic explanation for the results was used to devise a possible mechanism with its intermediates.

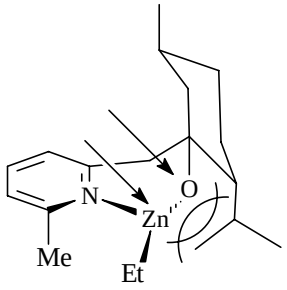


Ph$_{out}$ **6.15**-*anti* Ph$_{in}$ **6.15**-*anti* Ph$_{in}$ **6.15**-*syn* Ph$_{out}$ **6.15**-*syn*

Addition of diethylzinc to the pyridine alcohol *cis*-**2.3g** leads to the deprotonation of the hydroxyl group forming a six-membered intermediate in which the zinc is also coordinated to the pyridine nitrogen. The most probable conformation of the menthyl moiety is that the cyclohexane ring attains a chair conformation with the methyl, isopropyl and benzyl groups in an equatorial position and the hydroxylate in an axial position. The boat conformation of the nitrogen-zinc-oxygen ring is forced, by steric hindrance of the menthyl moiety and the pyridine ring, to attain such a conformation that the oxygen and the menthyl carbon-atom are below the plane of the pyridine ring. The ethyl-group on the zinc atom is forced upwards by steric interactions with the pyridine methyl. Complexation of a second equivalent of diethylzinc and of the aldehyde theoretically leads to the formation of **6.15**-*syn* or **6.15**-*anti*

both in the Ph_{in} and Ph_{out} forms. In the **6.15**-*anti* structures steric hindrance between the isopropyl group and the bridging ethyl group is expected. Because of this steric hindrance this structure will contribute to a minor extent in the formation of the product **6.2a**. The structures **6.15**-*syn* lack this steric hindrance, though steric repulsion between the pyridine methyl and the Ph of the aldehyde in the structure Ph_{in} **6.15**-*syn* also disfavors this intermediate structure. These unfavorable interactions are absent in the Ph_{out} **6.15**-*syn* structure, which therefore is expected to contribute mostly in the formation of the alcohols **6.2a**. After addition of the ethyl group to the aldehyde in the intermediate structure Ph_{out} **6.15**-*syn* the S-conformation of the product **6.2a** is formed in accord with the catalytic reactions.

Compound *trans*-**2.3g** was found to have no catalytic activity in the addition of diethylzinc to aldehydes. By having a closer look at the proposed intermediate this observation can be explained. Addition of diethylzinc to the pyridine alcohol *trans*-**2.3g** leads to the deprotonation of the hydroxyl group forming a six-membered intermediate **6.16**. The conformation that is attained by the menthyl moiety has the methyl, isopropyl and hydroxylate in an equatorial position and the benzylic group in an axial position. The boat conformation of the nitrogen-zinc-oxygen ring is forced by interference of the isopropyl group and the pyridine ring to attain a conformation in which the oxygen and the menthyl carbon-atom are above the plane of the pyridine ring. Addition of the aldehyde to the zinc leads to a shielding of the oxygen and addition of another equivalent of diethylzinc leads to shielding of the other zinc. Hence a complete transition structure can not be obtained.



6.16

6.1.5 Conclusions.

Application of the pyridine alcohols and thiols in a combinatorial approach of the diethylzinc addition led to interesting results. Moderate enantiomeric excesses were obtained in the screening of four different aldehydes. The enantiomeric composition of the reaction mixture was analyzed by means of chiral GC. Based on experimental data from literature a rational explanation for the enantiomeric outcome in the use of *cis*-**2.3g** as ligand was proposed. With the postulated intermediate structure it was also possible to explain the inactivity of the *trans*-**2.3g** ligand. The pyridine diols **2.1e** and *cis*-*cis*-**2.1g** were found to be

completely inactive whereas the dithiol **3.1f** was found to give the alcohols only in very low yield. A tightly bound zinc ion in the cavity of the ligands is thought to be the reason for this.

6.2 Pyridine Diols as Polymerization Catalyst.

6.2.1 Introduction.

Over the past decades many advances have been made in designing new olefin polymerization catalysts that have maximum control over the polymerization process.[24] As a result metallocene catalysts have been developed for the stereospecific polymerization of α-olefins. By tuning the geometry of the active site by means of structural changes on the ligand bound to the electrophilic metal ion, the microstructure of the resulting polymer can be controlled efficiently.[24a,f] Non-cyclopentadienyl based ancillary ligand systems are attracting increasing interest. These ligands give rise to new olefin polymerization catalysts that can have interesting polymerization properties.[24d-e,25] Only few examples are known of complexes with non-cyclopentadienyl based ligand systems that are able to control the stereochemistry of the resulting polymer as do many of their metallocene counterparts.[25a,e]

The use of pyridine diols as polymerization catalyst has been reported before; with metals like Zr and W active catalysts are formed.[26] With the use of the chiral pyridine diol **2.1g** we hoped to synthesis a chiral dibenzyl zirconium compound that can induce isotactic polymerization. Dianionic tridentate ligands can bind to group 4 metals in a facial or a meridional bonding mode depending on the donor function, the rigidity of the backbone and the steric demand of the substituents on the anionic functions (Figure 6.1).[24e, 27] Ligands with a pyridyl unit as σ-donor as well as ligands with large substituents on the anionic functions are preferably meridionally bound. The pyridine-diolate ligand is therefore likely to bind in a meridional conformation. This will induce a C_2-symmetric coordination sphere at the metal center comparable to the ansa-metallocene complexes that are used as precursors for the isotactic polymerization of α-olefins.

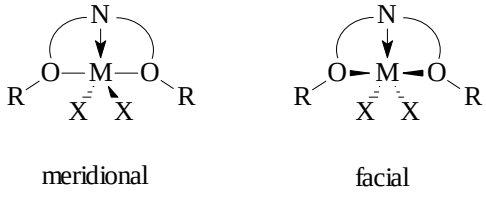
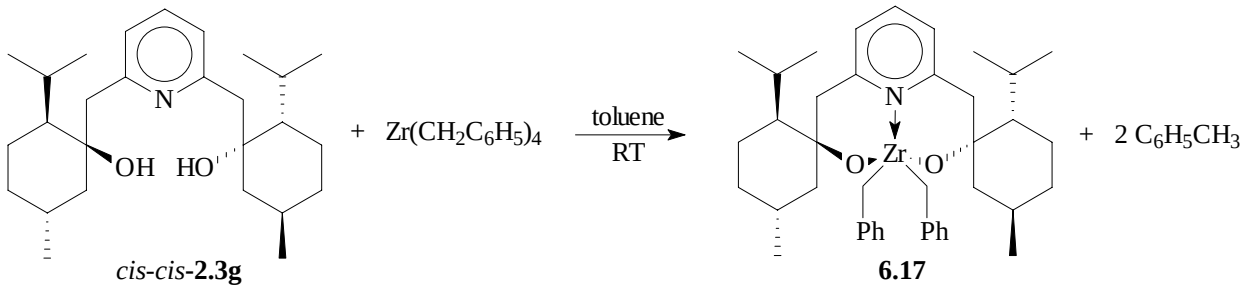


Figure 6.1 *Meridional and facial binding of dianionic tridentate pyridine diol **2.1g**.*

6.2.2 Results and Discussion.

Treatment of a toluene solution of tetrabenzyl zirconium with the neutral pyridine diol *cis-cis*-**2.1g** at room temperature leads to the formation of *cis-cis*-**2.1g**·$Zr(CH_2C_6H_5)_2$ **6.17** (Scheme 6.5). Cooling a pentane solution of compound **6.17** to –60°C results in precipitation of a yellow solid, which was isolated in a 50% yield. The modest isolated yield of the compound is caused by its high solubility. This resulted in a significant loss of product during work-up procedures. The formation of compound **6.17** in d_8-toluene was followed by ^{1}H NMR spectroscopy. This revealed the quantitative formation of compound **6.17**.



cis-cis-**2.3g** **6.17**

Scheme 6.5 *Complexation of tetrabenzyl zirconium with diol cis-cis-**2.3g**.*

The ^{1}H NMR spectrum of the compound at room temperature shows one set of doublets at 2.96 and 2.33 ppm for the diastereotopic pyridine methylene protons of the backbone of the ligand and two doublets at 2.59 and 2.24 ppm for the benzyl methylenes. Furthermore, one set of signals is observed for the menthyl protons. This reveals a C_2-symmetric binding of the ligand to the metal center. This can be the result of a meridional binding of the ligand or a rapid interconversion of the two possible fac-isomers.[27b] At low temperature (-60°C) a second set of signals for the menthyl protons appear. This is probably caused by a ring-inversion process rather than the above mentioned interconversion, because the resonances for the pyridine and bridge protons remain virtually unchanged.

Compound **6.17** was studied with semi-empirical calculations using a PM3(tm) model (Figure **6.2**).[28] This suggested a distorted trigonal bipyramidal geometry of the metal center with the anionic functions at the axial positions. The calculated structure is in agreement with NOESY spectroscopy. In the NOESY spectrum a long-range interaction was observed for the *i*-propyl methyn with the pyridine methylene protons, and for the *i*-propyl methyl with both the methylene and the aryl of the benzyl ligand.

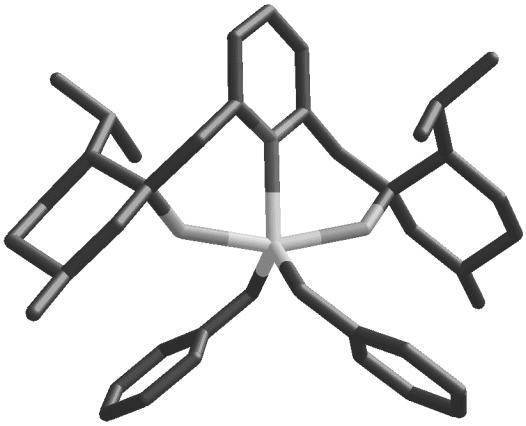
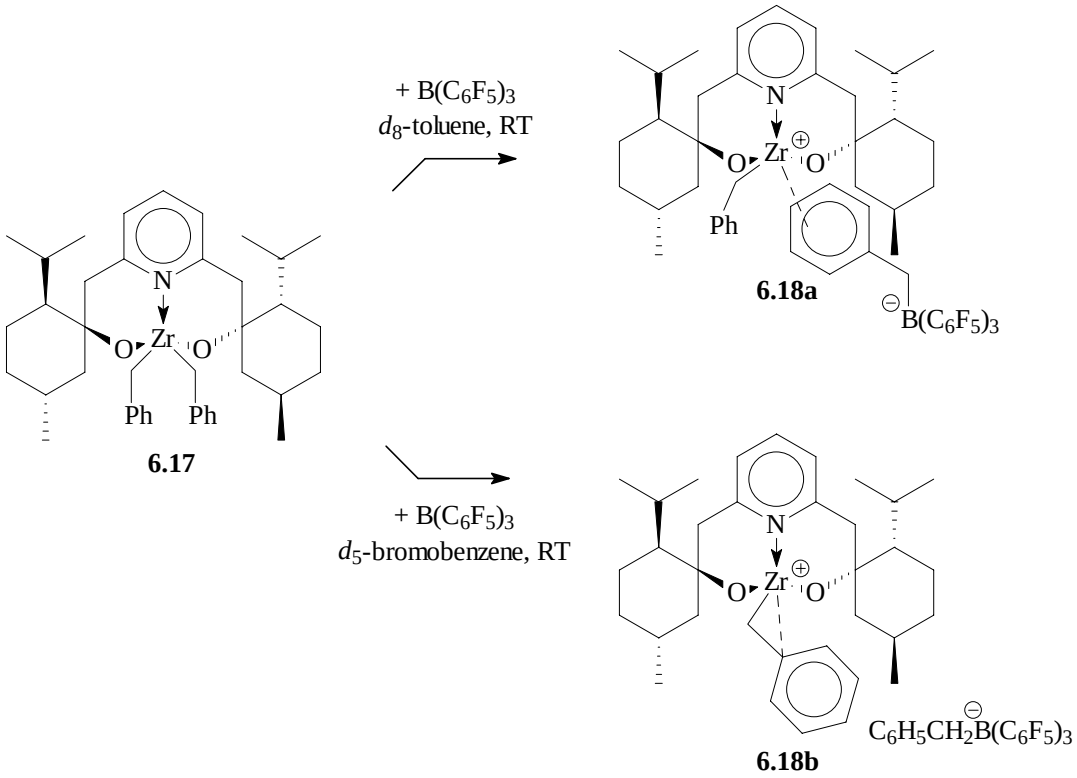


Figure 6.2 *Result of semi-empirical calculations using a PM3(tm) model.*

Addition of a d_8-toluene solution of compound **6.17** to one equivalent of tris(pentafluorophenyl)borane results in the abstraction of a benzyl ligand by the Lewis-acidic borane yielding {**2.3g**·$ZrCH_2C_6H_5$}{η^6-$C_6H_5CH_2B(C_6F_5)_3$} (**6.18a**, Scheme 6.6).



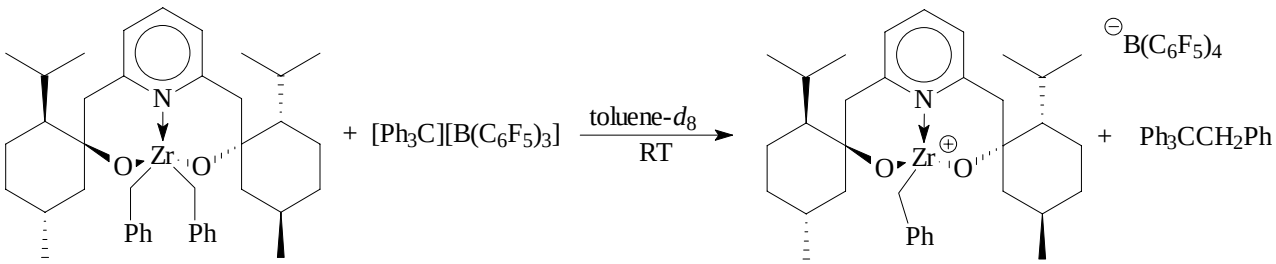
Scheme 6.6 *Formation of the close contact ion pair **6.18a** and the solvent separated ion pair **6.18b**.*

The ^{1}H NMR spectrum of the pale-yellow reaction mixture at room temperature in d_8-toluene reveals resonances for the aryl protons of the benzyl borate anion at 6.7 and 5.94 ppm. These resonances are shifted upfield compared to compound **6.17**, suggesting an η^6-

coordination of the aryl group of the borate anion to the cationic zirconium complex. The formation of a contact ion pair is in agreement with observations made in the ^{19}F NMR spectrum of compound **6.18a**. The difference in chemical shift of the *para* and *meta* fluorine resonances is 4.06 ppm.[29] In the ^{1}H NMR spectrum two broad resonances at 3.5 and 3.6 ppm are observed for the two diastereotopic methylene protons of the anion. The methylene carbon of the zirconium bonded benzyl group shows a resonance at 71 ppm with a J_{CH} coupling constant of 117.4 Hz. This benzyl ligand is thus η^1-bonded to the metal center.

When the reaction is repeated in d_5-bromobenzene, a solvent separated ion pair is formed instead of a contact ion pair (**6.18b**, Scheme 6.6). The ^{19}F NMR spectrum of the compound reveals a $\Delta\{\delta(m\text{-F}),\delta(p\text{-F})\}$ of 2.76 ppm for the benzyl borate anion.[29] In this case, the electron deficient metal center is stabilized by η^2-bonding of the remaining benzyl ligand. The ^{13}C NMR spectrum of compound **6.18b** shows a resonance for the methylene of the benzyl ligand at 69.42 ppm (J_{CH}= 142.3 Hz).

Another route to a solvent separated ion pair is the reaction of compound **6.17** with trityl tetrakis(pentafluorophenyl)borate in d_8-toluene (Scheme 6.7). The trityl reagent abstracts a benzyl ligand resulting in $\{$**2.3g**$\cdot Zr(CH_2C_6H_5)\}\{B(C_6F_5)_4\}$ and 1,1,1,2-tetraphenylethane. Even though the ^{1}H NMR spectrum of the compound is not conclusive, the ^{19}F NMR spectrum consists of three distinct resonances that are consistent with the tetrakis(pentafluorophenyl)borate anion. This counter ion is considered to be weakly coordinating.[30]



6.17 **6.19**

Scheme 6.7 *Formation of the solvent separated ion pair **6.19**.*

6.2.3 Polymerization Experiments with α-Olefins.

A propene polymerization experiment in toluene at 0°C (2 bars of propene, compound **6.19** as a catalyst) resulted in fully atactic polypropene. The productivity of the catalyst is 900 $g\cdot mol^{-1}\cdot h^{-1}$. The resulting polymer has a molecular weight of ~8000 with a polydispersity of 1.7. A small fraction of high molecular weight polypropene is formed as well (Mw = $1.5\cdot10^6$; PDI=1.3).

When compound **6.18a** in an NMR tube was treated with a large excess of 1-hexene in a high concentration the reaction mixture turned highly viscous. ^{1}H NMR spectroscopy revealed the conversion of the monomer to poly(1-hexene). A propene polymerization experiment with compound **6.18a** as a catalyst using the same conditions as described above for **6.19** did not yield the polymer. This could be an effect of the lower concentration compared to the hexene polymerization.

6.2.4 Conclusions.

Treatment of tetrabenzyl zirconium with pyridine diol *cis*-*cis*-**2.1g** yields the corresponding bisbenzyl zirconium complex **6.17**. Various NMR spectroscopic studies together with semi-empirical calculations reveal a C_2-symmetric binding of the ligand to zirconium. The reaction of the compound with tris(pentafluorophenyl)borane results in the formation of a cationic benzyl complex **6.18**. In d_8-toluene, the benzylborate anion is coordinating to the metal center giving complex contact ion pair **6.18a**. Abstraction of the benzyl ligand in d_5-bromobenzene afforded the solvent separated ion pair. **6.18b**. A similar ion pair was prepared using tetrakis(pentafluorophenyl)borate in d_8-toluene. Application of these complexes in the polymerization of propene was successful for **6.19** but failed for **6.18a**. However, this complex was capable of polymerizing 1-hexene. Polymerization of propene with this pyridine diol as ligand unfortunately led to atactic polymer. This suggests a rather open coordination sphere of the metal center. The absence of sufficient steric bulk of the menthone unit or the high fluxionality of the ligand makes the system unsuitable for the stereospecific polymerization of α-olefins.

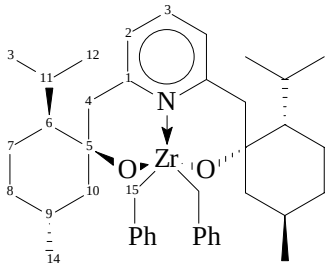
6.3 Experimental Section.

General Remarks: See Chapter 2. All reactions concerning the polymerization catalyst were carried out by Marco Bouwkamp. These reactions were carried out under nitrogen atmosphere using standard Schlenk-line and glovebox techniques. Reagents were purchased from commercial suppliers and used without further purification, unless stated otherwise. $Zr(CH_2C_6H_5)_4$ were prepared according to literature procedures.[31] Except for d_5-bromobenzene (dried on 4Å molsieves) the solvents were dried by distillation from Na/K alloy at nitrogen atmosphere.

General procedure for Et_2Zn addition to the aldehyde mix: To a solution of the ligand (4.0 μmol) in 2 mL of toluene was added Ti(O*i*Pr)$_4$ (1M, 0.12 mmol) and the mixture was stirred for 30 min at 40°C. After cooling to –40°C diethylzinc (1M solution in hexanes; 0.22 mmol) was added. The mixture was stirred for 30 min and the mixture of aldehydes in 1 mL of toluene was added (25 μmol per aldehyde, 0.1 mmol in total). The mixture was allowed to

reach –20°C and stirred for 18h. The reaction was quenched with NH_4Cl and extracted twice with ethyl acetate. The organic phase was dried and a sample of 0.2 μL was subjected to GC analysis (capillary column: hydrodex-β-3P; 25 m x 0.25 mm; oven temperature 55°C + 1.5°C/min ↑ to 150°C; injector temperature 250°C; detector temperature 250°C; cowman head pressure 120 kPa). T_R of **6.1a** 17.7 min; **6.1b** 20.2 min; **6.1c** 37.9 min; **6.1d** 39.9 min; **6.2a**(S) 39.7 min, **6.2a**(R) 40.3 min; **6.2b**(R) 46.5 min, **6.2b**(S) 47.4 min; **6.2c**(S) 56.7 min, **6.2c**(R) 56.8 min; **6.2d**(R) 63.0 min, **6.2d**(S) 64.6 min..

***Cis-cis*-2.1g·Zr($CH_2C_6H_5$)$_2$ 6.17**. To a Schlenk vessel charged with $Zr(CH_2C_6H_5)_4$ (529 mg, 1.16 mmol) in 25 mL of toluene and a stirbar, a 25 mL solution of *cis-cis*-**2.1g** (480 mg, 1.16 mmol) in toluene was added while stirring. This resulted in a pale yellow solution. After stirring for 15 minutes at room temperature, the solvent was removed at reduced pressure. The compound was extracted twice with 20 mL of pentane. The combined organic layers were cooled to –60 °C. The compound precipitated yielding **6.17** after decanting the supernatant solution and evaporating the solvents at reduced pressure (401 mg, 0.58 mmol, 50%). ^{1}H NMR (Figure 6.3, d_6-benzene, 300MHz, RT) δ 7.1 (m, 6H, *m*-Ph, *p*-Ph), 6.9 (m, 4H, *o*-Ph), 6.90 (t, J_{HH} = 7.5 Hz, 1H, H_3), 6.44 (d, J_{HH} = 7.7 Hz, 2H, H_2), 2.96 (d, J_{HH} = 13.9 Hz, 2H, H_4), 2.59 (d, J_{HH} = 9.2 Hz, 2H, H_{15}), 2.33 (d, J_{HH} = 13.9 Hz, 2H, H_4), 2.24 (d, J_{HH} = 9.2 Hz, 2H, H_{15}), 2.08 (d sept, J_{HH} = 1.8, 6.7 Hz, 2H, H_{11}), 1.9 (m, 2H, H_9), 1.7-1.9 (m, 4H, H_8, H_7), 1.5-1.6 (m, 2H, H_7), 1.2-1.4 (m, 2H, H_{10}), 1.08 (d, J_{HH} = 6.6 Hz, 6H, $H_{12/13}$), 1.0 (m, 2H, H_6), 0.95 (d, J_{HH} = 7.0 Hz, 6H, $H_{12/13}$), 0.90 (t, J_{HH} = 7.1 Hz, 2H, H_8), 0.85 (d, J_{HH} = 6.6 Hz, 6H, H_{14}), 0.73 (t, J_{HH} = 12.5 Hz, 2H, H_{10}); ^{13}C NMR (d_6-benzene, 125 MHz, RT) δ 161.83 (s, $C_{q\text{-}Ph}$), 144.53 (s, C_1), 138.57 (d, J_{CH} = 158.4 Hz, *o*-Ph), 130.90 (d, J_{CH} is not determinable due to overlap, *m*-Ph), 128.10 (d, J_{CH} is not determinable due to overlap, *p*-Ph), 124.72 (d, J_{CH} = 164.8 Hz, C_2), 121.94 (d, J_{CH} = 161.1 Hz, d, C_3), 79.99 (s, C_5), 58.26 (t, J_{CH} = 128.2 Hz, C_{15}), 52.33 (d, J_{CH} = 129.2, C_6), 51.70 (t, J_{CH} = 104.4 Hz, C_4), 48.97 (t, J_{CH} = 121.5 Hz, C_{10}), 35.86 (t, J_{CH} = 124.5 Hz, C_8), 28.32 (d, J_{CH} = 129.4 Hz, C_9), 26.10 (d, J_{CH} = 124.5 Hz, C_{11}), 24.95 (q, J_{CH} = 125.8 Hz, $C_{12/13}$), 23.01 (t, J_{CH} = 126.3 Hz, C_7), 22.77 (q, J_{CH} = 124.5 Hz, C_{14}), 19.45 (q, J_{CH} = 126.2 Hz, $C_{12/13}$). Anal. Calcd for $C_{41}H_{57}NO_2Zr$: C, 71.67; H, 8.30; N, 2.04; Zr, 13.28. Found: C, 71.45; H, 8.45; N, 1.92; Zr, 13.18.



6.17

{*cis-cis*-2.1g·Zr($CH_2C_6H_5$)}{η^6-$C_6H_5CH_2B(C_6F_5)_3$} **6.18a**. A solution of [*cis-cis*-**2.1g**·$Zr(CH_2C_6H_5)_2$ (27.2 mg, 40 μmol) in 0.7 mL of d_8-toluene was added to $B(C_6F_5)_3$ (20.0 mg, 39 μmol). The reaction mixture was transferred to an NMR tube. ^{1}H NMR (d_8-toluene, 500 MHz, RT) δ 7.3 (m, 2H, *o*-ZrBz), 7.0 (m, 3H, *m*-ZrBz, *p*-ZrBz), 6.84 (t, 1H, J_{HH} = 7.8 Hz, *p*-Py), 6.7 (m, 3H, *m*-BBz, *p*-BBz), 6.4 (d, 2H, J_{HH} = 7.7 Hz, *o*-Py), 5.94 (d, 2H, J_{HH} = 7.0 Hz, *o*-BBz), 3.6 (br, 1H, BCH_2), 3.5 (br, 1H, BCH_2), 2.6 (br d, J_{HH} = 13.6 Hz, 1H,

$ZrCH_2$), 2.1 (partly covered by solvent resonances, 1H, $ZrCH_2$), 0.3-2.5 (multiple broad resonances for the menthone group); ^{19}F NMR (d_8-toluene, 188 MHz, RT) δ -125.46 (d, J_{FF} = 20.3 Hz, *o*-F), - 162.32 (t, J_{FF} = 20.3 Hz, *p*-F), - 166.38 (d, J_{FF} = 19.2 Hz, *m*-F).

{*cis-cis*-2.1g·Zr(η^2-$CH_2C_6H_5$)}{$C_6H_5CH_2B(C_6F_5)_3$} 6.18b. To $B(C_6F_5)_3$ (21 mg, 41 μmol) a solution of *cis-cis*-**2.1g**·$Zr(CH_2C_6H_5)_2$ (27.6 mg, 40 μmol) in 0.7 mL of d_5-bromobenzene was added. The pale-yellow solution was transferred to an NMR tube. ^1H NMR (500 MHz, d_8-toluene, -40°C, two conformations) δ 7.3, 7.2, 7.0 (multiplets partly covered by solvent resonances, ZrBz and BBz), 6.9 (covered by solvent resonance,1H, *p*-Py), 6.83 (d, 1H, J_{HH} = 7.1 Hz, *p*-Py), 6.6 (br, 2H, *o*-Py), 6.4 (br, 2H, *o*-Py), 3.5 (br, 4H, BCH_2), 3.23 (br d, 1H, J_{HH} = 13.2 Hz, H_4), 2.96 (br d, 1H, J_{HH} = 14.8 Hz, H_4), 2.85 (br d, 1H, J_{HH} = 14.8 Hz, H_4), 2.7 (br, 1H, ZrBz), 2.6 (br, 1H, ZrBz), 2.42 (br d, 1H, J_{HH} = 13.6 Hz, H_4), 1.9 (m, 2H, H_{11}), 1.5 (m, 2H, H_9), 0.1-1.6 (multiple broad resonances for the menthone group); ^1H NMR (500 MHz, d_8-toluene, RT) δ 7.4, 7.2, 7.0 (multiplets partly covered by solvent resonances, ZrBz and BBz), 6.8 (m, 1H, *p*-Py), 6.7 (br, 2H, *o*-Py), 3.4 (br, 2H, BBz), 2.61 (dd, 2H, J_{HH} = 23.9 Hz, ZrBz), 0.1-3.4 (multiple broad resonances for the menthone group and the methylene of the backbone of the ligand); ^{19}F NMR (d_8-toluene, 188 MHz, RT) δ -131.18 (d, J_{FF} = 22.5 Hz, *o*-F), -164.36 (br, *p*-F), -167.17 (br, *m*-F).

{*cis-cis*-2.1g·Zr($CH_2C_6H_5$)}{$B(C_6F_5)_4$} 6.19. A solution of *cis-cis*-**2.1g**·$Zr(CH_2C_6H_5)_2$ (6.9 mg, 10 μmol) in 0.7 ml of d_8-toluene was added to trityl tetrakis(pentafluorophenyl)borate (9.0 mg, 9.8 μmol). The reaction mixture was transferred to an NMR tube; $^{19}F\{^1H\}$ NMR (d_8-toluene, 188 MHz, RT) δ -132.64 (br, *o*-F), -163.54 (t, J_{FF} = 20.8 Hz, *p*-F), -167.66 (br, *m*-F).

Polymerization of propene with 6.19. An autoclave was charged with *cis-cis*-**2.1g**·$Zr(CH_2C_6H_5)_2$ (6.7 mg, 9.8 μmol), trityl tetrakis(pentafluorophenyl)borate (9.2 mg, 9.9 μmol) and a stirrbar. To the reactants 6.5 mL of toluene was added, yielding a brown-yellow oil. The reaction mixture was exposed to 2 bars of propene during one hour, while stirring at 0°C. The reaction mixture was quenched with 5 mL of methanol. The solvents were removed by rotary evaporation and the product was dried at 80°C and reduced pressure, yielding 1.37 g of polypropene. Activity: 0.9 $kg \cdot mol^{-1} \cdot h^{-1}$; Mw = 8000

Polymerization of 1-hexene with 6.18a. An excess of 1-hexene (0.2 mL, 3.5 mmol) was added to a solution of {**2.3g**·$Zr(CH_2C_6H_5)$}{η^6-$C_6H_5CH_2B(C_6F_5)_3$} (18 μmol) in d_6-benzene (prepared *in situ*). The 1-hexene was converted to poly(1-hexene) according to NMR.

Polymerization of propene with 6.18a. To of tris(pentafluorophenyl)borane (5.0 mg, 9.8 μmol) and *cis-cis*-**2.1g**·$Zr(CH_2C_6H_5)_2$ (6.8 mg, 9.9 μmol) were added in 6.5 mL of toluene.

The reaction mixture was exposed to 2 bars of propene during one hour, while stirring at RT. No consumption of propene was observed.

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28 Semi-empirical calculations were made with SPARTAN™ using a PM3(tm) model. Various structures with the ligand bonding meridional to zirconium, the menthone group in a boat and a chair configuration, and the benzyl ligands in different conformations were optimized. Of these calculations, the depicted structure is second lowest in energy (difference with the lowest conformation = 1.3 kJ/mol). This structure, however, is consitent with observations from NOESY spectoscopy.

29 A difference in chemical shift between the *m*-F and *p*-F resonances in the ^{19}F NMR spectrum for an alkyl tris(pentafluorophenyl)borate anion of <3 ppm is indicative for a non-coordinated anion, whereas a difference of 3-6 ppm is observed for coordinating counterions. Horton, D. A. *Organometallics* **1996**, *15*, 2675.

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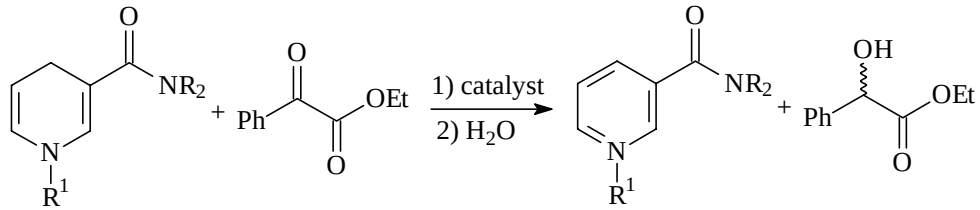
CHAPTER 7

Pyridine Thiols as Models for HLADH.

Abstract: The zinc complex of pyridine dithiol **3.1f** was tested as a model for the active site of the enzyme horse liver alcohol dehydrogenase and was found to be unsuccessful. The reason for this probably is the incapacity of zinc to coordinate the 1,4-dihydropyridine as well as the substrate at the same time. A mimic system **7.5** was designed in which a 1,4-dihydropyridine is attached to the pyridine thiol. This system indeed is capable of reducing ethyl phenylglyoxylate in moderate yield and low enantioselection. The results were compared to the model system **7.14** based on a pyridine alcohol. Like the thiol system **7.5** this system was found to reduction of the ketone **7.2**, but the ketone is slowly oxidized back to the alcohol. The pyridinium salt **7.13**, was also found to oxidize the alcohol **7.4** in the presence of $Mg(ClO_4)_2$. For the thiol and alcohol systems **7.5** and **7.13** it remains unclear whether or not the reaction goes to completion. It might be due to decomposition of the catalyst or to an equilibrium that has been reached in the reaction.

7.1 Introduction.

Horse liver alcohol dehydrogenase (HLADH) is a zinc-containing enzyme that is capable of reducing ketones and oxidizing alcohols making use of the coenzyme NADH. Mimicking the activity of HLADH has been a subject of study in our group for a number of years.[1] Some interesting models, which mimic the activity of HLADH, have been developed. Most of these models are based on 1,4-dihydropyridines (as discussed in Chapter 1). These substituted dihydropyridines that have been used are capable of reducing activated carbonyl compounds like trifluoroacetophenone, pyridine-2-carboxaldehyde, benzophenone, and ethyl phenylglyoxylate.[2] Of the dihydropyridines used, the N-alkylated 1,4-dihydronicotinamides show the greatest resemblance to NADH and have greater reactivity than others models. These compounds, however, are sensitive to side reactions.[3] The combination of a 1,4-dihydronicotinamide derivative **7.1** with ethyl phenylglyoxylate **7.2** has been used as model reaction to study catalysts as models for the NADH system (Scheme 7.1).[4] The reaction is usually carried out with a metal salt activator like $Mg(ClO_4)_2$ or $Zn(ClO_4)_2$. Reactions with these metal ions, however, are stoichiometric rather than catalytic. With europium or neodynium the reaction proceeds catalytically.[5] Reaction without a metal ion is minimal.

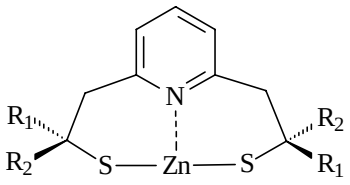


7.1 **7.2** **7.3** **7.4**

Scheme 7.1 *The model reaction.*

7.2 Model Compounds.

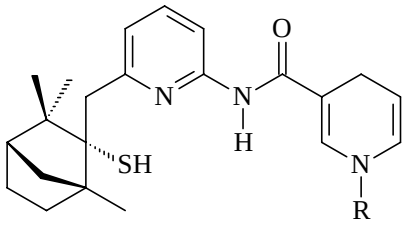
Models that mimic both the (re)activity as well as the structural aspects of the active site of the enzyme HLADH are not available. Attempts to use the monomeric zinc complex **4.5d** of pyridine dithiol **3.1d** failed due to the instability of this complex.[6] A more stable monomeric zinc complex **4.5f** was formed with pyridine dithiol **3.1f** (for details see Chapter 4).



4.5d,f

d: R_1,R_2 = fluorenyl
f: R_1,R_2 = fenchyl

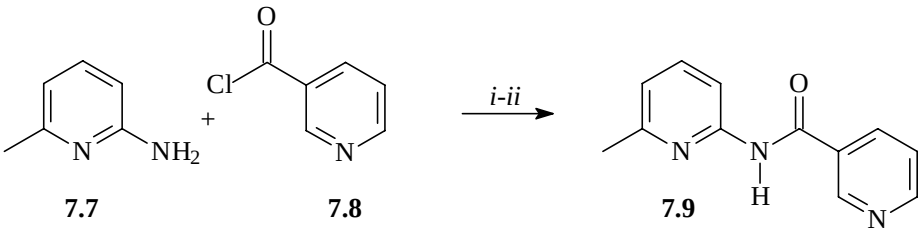
Application of this monomeric zinc complex as catalyst in the model reaction depicted in Scheme 7.1 using *N*-benzy-1,4-dihydronicotinicamide (R^1=Bz, R=H) as cofactor, however, did not lead to the reduction of ethyl phenylglyoxylate. One possible reason for the failure of this complex is that it is not able to coordinate with the substrate as well as with the 1,4-dihydropyridine. On the one hand the vicinity of the 1,4-dihydropyridine is necessary to accomplish reduction of the substrate. On the other hand substrate binding to the metal center is necessary to activate the carbonyl bond. In the natural enzyme NADH is closely situated to the zinc containing active site to which the substrate binds. All components are centralized in the active site and reaction therefore can take place. In our artificial system these components are close together and reaction cannot occur. In order for an artificial system to work like the enzyme the components should be brought together more efficiently. This can be accomplished by linking one or more components. By attaching the 1,4-dihydropyridine to a pyridine thiol a system (structure **7.5**) is obtained in which the 1,4-dihydropyridine and the thiol functionality are always close together. Coordination of the substrate to the zinc complex of this system now should lead to the desired reduction of the substrate.



7.5

7.3 Synthesis of the Model Compounds.

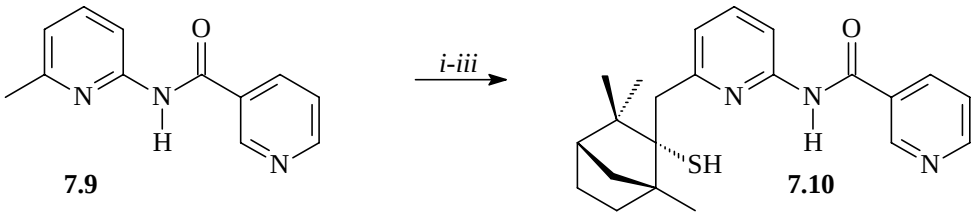
The model system **7.5** was synthesized starting from 2-amino-picoline **7.7** and nicotinic acid **7.6**. Attempted coupling of these starting materials to obtain the dipyridine **7.9** with DCC failed due to stability of the intermediate in which the acid is coupled to the DCC. To bypass the complication the nicotinic acid was converted to its acid chloride[7] **7.8** and allowed to react with 2-amino-picoline in the presence of pyridine to trap the HCl formed (Scheme 7.2). The use of other bases instead of pyridine gave rise to lower yields of the bipyridine adduct **7.9**.



7.7 **7.8** **7.9**

Scheme 7.2 *Reagents and conditions*: *i*, pyridine, CH_2Cl_2, 0°C; *ii* 2 N NaOH.

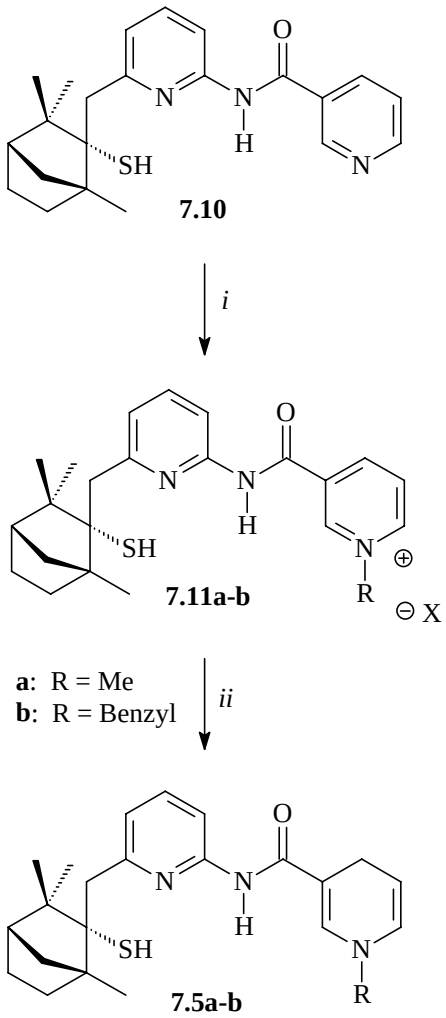
The bipyridine adduct **7.9** was deprotonated using 2.5 equivalents of potassium diisopropylamide in order to deprotonate the methyl group. The deprotonation was followed by the addition of (*R*)-thiofenchone to give the pyridine thiol adduct **7.10** after hydrolysis (Scheme 7.3). Deprotonation of the bipyridine adduct **7.9** with *n*-butyllithium failed due to the directing *ortho* metalation effect of the amide functionality. This functionality effectuates deprotonation at positions adjacent to the amide at both pyridine rings.[8] Using KDA no directing *ortho* metalation effect is presence and deprotonation occurs selectively on the methyl group.



7.9 **7.10**

Scheme 7.3 *Reagents and conditions*: *i*, KDA, -70°C; *ii* (*R*)-thiofenchone; *iii* NH_4Cl.

The pyridine thiol derivative **7.10** subsequently was alkylated in acetonitrile with methyliodide in the presence of $LiClO_4$ to afford the soluble pyridinium perchlorate salt **7.11a** (Scheme 7.4). Methylation of the nicotinic nitrogen occurred selectively. No methylation of the other pyridine nitrogen or the thiol group took place. This might be due to shielding of this pyridine ring by hydrogen bonding of the thiol group. Selective alkylation of the nicotinic nitrogen with benzyl bromide was accomplished at room temperature in dichloromethane affording the pyridinium bromide **7.11b**. Again no alkylation of the other pyridine nitrogen or thiol was observed under these conditions.



Scheme 7.4 *Reagents and conditions*: *i,* MeI, $Mg(ClO_4)_2$, CH_3CN or benzylbromide, CH_2Cl_2; *ii* $Na_2S_2O_4$, phosphate buffer pH=7.00.

The pyridinium ion **7.11a** was reduced to the corresponding 1,4-dihydropyridines **7.5a** in a diluted buffered (pH = 7.0) solution using excess of $Na_2S_2O_4$ as reductant. Although $Na_2S_2O_4$ cleanly gives reduction to the 1,4-dihydropyridines at higher concentrations of **7.11** also the 1,6-dihydropyridines are formed. This probably is due to hydride exchange of the 1,4-dihydropyridine with the unreduced pyridine adducts present. The pyridinium adduct **7.11b** was reduced with $Na_2S_2O_4$ in a buffered solution giving cleanly the 1,4-dihydropyridine **7.5b.** Both dihydropyridines are relatively unstable and had to be used immediately after workup.

7.4 Test Results with the Model Compounds.

When 1,4-dihydropyridine **7.5a** was applied in the reduction of ethyl phenylglyoxylate in the presence of $Mg(ClO_4)_2$, which is the most common metal salt activator, the reaction proceeded quickly and after only 15 min 30% of the substrate has been

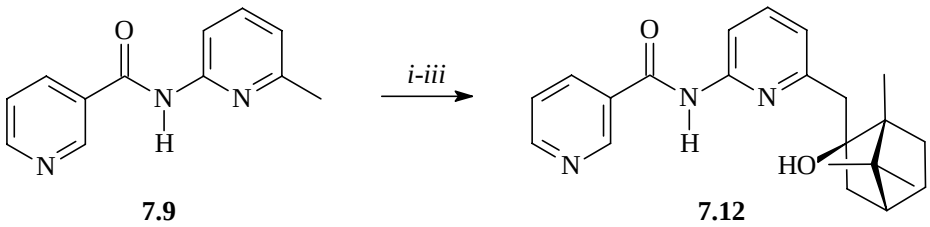
reduced (Table 7.1). Stirring the mixture for a longer time did not lead to a higher conversion. Determination of the enantiomeric excess revealed a low ee of 9.6%. Reaction at a lower temperature led to a drop in reaction rate and to a small increase in the enantioselection. Compared to known examples in literature this system is relatively fast in the reduction reaction (for a summary see Chapter 1). Most systems require reaction times of days, whereas some are known to give an equally rapid reaction. When the reduction of the ketone was carried out in the presence of $Zn(ClO_4)_2$ at room temperature the reduction also took place, although it proceeded slower compared to the magnesium catalyzed reaction. The product, however, was formed as the other enantiomer in a slightly higher enantiomeric excess. This can be due to a different coordination of the zinc compared to the magnesium. Zinc easily binds sulfur, whereas magnesium tends to complex harder atoms like oxygen.[9] At 0°C a decrease in reaction rate is observed, whereas the enantioselectivity almost stays the same. Again, conversion of the ketone was not complete. The instability of the catalyst might be an explanation for this; it is also possible that an equilibrium was reached. When the benzyl-adduct **7.5b** was applied in the reduction similar results were obtained, that is to say, a fast reduction and moderate yields with a low e.e. The combination of this system **7.5** in the presence of zinc as metal salt activator give a fair, though not perfect, representation of the active site of HLADH.

Table 7.1 Results of the reduction of ethyl phenylglyoxylate.

			RT			0°C	
Dihydropyridine	metal	time	e.e.	yield	time	e.e.	yield
7.5a	$Mg(ClO_4)_2$	15 min	9.6 (R)	30%	60 min	14.1 (R)	34%
	$Zn(ClO_4)_2$	60 min	18.7 (S)	16%	2h	19.0 (S)	15%
7.5b	$Mg(ClO_4)_2$	15 min	11.3 (R)	25%	-	-	

7.5 Other Derivatives as Models.

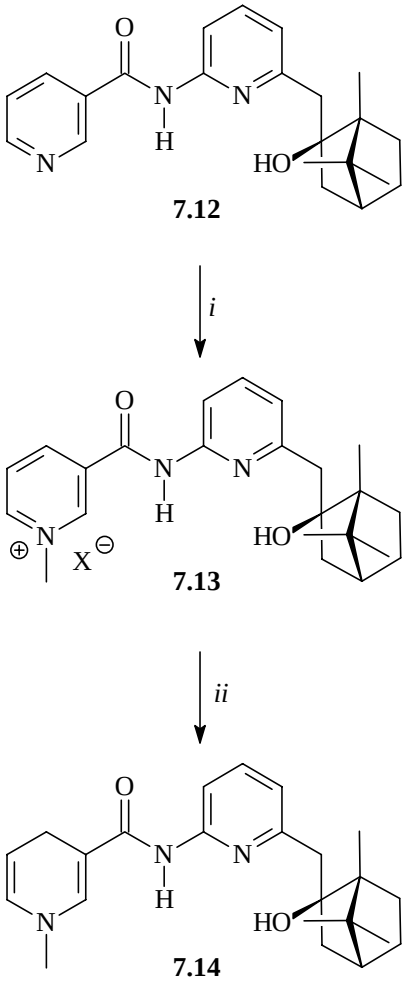
A model system that diverges more from the natural situation, was synthesized to investigate a possible positive effect of the thiol functionality in the model system **7.5**. To this purpose a model system based on a pyridine alcohol was synthesized. The lack of the thiol group is expected to lead to a different behavior of the model system in the test reaction. The model system was synthesized starting from the dipyridine **7.9** by deprotonation with KDA and reaction with (*R*)-camphor to afford **7.12** (Scheme 7.5). At low temperatures (–70°C) the competitive enolization of the camphor is reduced. Reaction at higher temperatures gives rise to a substantial loss of the desired product because of enolization of the camphor.



7.9 **7.12**

Scheme 7.5 *Reagents and conditions: i,* KDA, -70°C; *ii* (*R*)-camphor; *iii* NH_4Cl.

The adduct **7.12** is methylated selectively at the nicotinic pyridine ring with methyliodide to the pyridinium iodide salt **7.13** (Scheme 7.6). Conversion of this salt to the dihydropyridine was troublesome. Mixtures of 1,4 and 1,6-dihydropyridines were formed even when reduction was carried out in dilute solutions. However, conversion of the iodide salt **7.13** to the perchlorate salt prior to the reduction afforded the 1,4-dihydropyridine **7.14** selectively. The products was found to be unstable and had to be used in the test reaction immediately after the reduction.



Scheme 7.6 *Reagents and conditions: i,* MeI, $Mg(ClO_4)_2$, CH_3CN; *ii* $Na_2S_2O_4$, phosphate buffer pH=7.00.

Application of this model **7.14** in the reduction of ethyl phenylglyoxylate **7.2** in the presence of $Zn(ClO_4)_2$ did not lead to reduction of the substrate not even after 48h of stirring at room temperature. Reduction in the presence of $Mg(ClO_4)_2$ proceeded partly (15%) within 30 min, but after 2 h the alcohol began to be consumed and was converted to the ketone again. After 24 h only 5% of the alcohol was left. Addition of the pyridinium perchlorate salt **7.13** to a mixture of the alcohol and ketone (ratio 2:1) in the presence of $Mg(ClO_4)_2$ also led to the oxidation of the alcohol. After 18h the ratio was reduced to 1:1. The exact reason for the oxidation remains unclear, but it might be a consequence of the presence of perchloric acid after the formation of magnesium alkoxides.

7.6 Conclusions.

Attempts to obtain a model for the active site of HLADH based on the zinc complexes of pyridine dithiols **3.1** was not successful. The zinc seems to be incapable of coordinating the 1,4-dihydropyridine and substrate in the same time. Therefore a mimic **7.5** was designed in which a 1,4-dihydropyridine is attached to the pyridine thiol. This system indeed is able to reduce ethyl phenylglyoxylate in moderate yield and low enantioselection. The results were compared to the model system **7.14** based on a pyridine alcohol. This system was found to give scarcely any reduction of the ketone **7.2** but the pyridinium salt **7.13** was found to partly oxidize the alcohol **7.4**. For the thiol and alcohol systems **7.5** and **7.13** it remains unclear whether the reaction stopped because of the decomposition of the catalyst or whether a equilibrium has been reached in the reaction. More research has to be carried out to get a clear picture of the process.

7.7 Experimental Section.

General Remarks: See chapter 2.

***N*-(6-methyl-2-pyridinyl)nicotinamide 7.9.**

To a freshly prepared solution of nicotinic acid chloride[7] **7.8** (17.7 g, 0.1 mol) in 250 mL of dichloromethane at 0 °C was added pyridine (11.9 g, 0.15 mol). After stirring for 15 min 2-amino-picoline **7.7** (10.8 g, 0.1 mol) in 25 mL of dichloromethane was added at such a rate that the temperature did not rise above 5 °C. Stirring continued for 1 h and the mixture was quenched with 2N NaOH. The organic layer was separated and washed with brine, dried over Na_2SO_4. After removal of the solvent the product was recrystallized from ethanol/water (1:1) affording **7.9** as colorless crystals (17.7 g, 0.8 mmol, 83%): mp 143-144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 6.95 (d, *J* = 7.69 Hz, 1H), 7.42 (m, 1H), 7.65 (t, *J* = 7.69 Hz, 1H), 8.14 (d, *J* = 8.43 Hz, 1H), 8.21 (d, *J* = 5.86 Hz, 1H), 8.56 (br, NH), 8.77 (d, *J* = 5.12,

1H), 9.14 (s, 1H); ^{13}C NMR δ 23.52 (q), 111.36 (d), 119.78 (d), 123.36 (d), 129.99 (s), 135.11 (d), 138.94 (d), 148.39 (d), 150.40 (s), 152.60 (d), 156.73 (s), 163.94 (s); HRMS calcd 213.090, found 213.092. Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.29; H, 5.22; N, 19.30.

Preparation of KDA.[10]

To a cooled solution of 12.5 mmol potassium-*t*-butoxide and 12.5 mmol diisopropylamine in 50 mL of THF at –90 °C was slowly added 12.5 mmol n-BuLi (1.6M solution in hexane). This solution was stirred for 30 min at –80 °C and used immediately.

***N*-(6-[[(1*R*,2*R*)-1,3,3-trimethyl-2-sulfanylbicyclo[2.2.1]hept-2-yl]methyl]-2-pyridinyl)nicotinamide 7.10.**

A solution of **7.9** (2.56 g, 12 mmol) in 200 mL of THF was cooled to –70°C and KDA (0.25 M in THF, 116 mL, 29 mmol) was added. After stirring for 10 min (*R*)-thiofenchone (2.1 g, 12.5 mmol) in 5 mL of THF was added. The solution was stirred for an additional hour allowing the mixture to reach room temperature. Then 25 mL of 2N NH_4Cl was added to the mixture and it was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The product was purified by means of column chromatography (silica, ethyl acetate/hexane 1:2) affording **7.10** as a colorless solid (3.5 g, 9.2 mmol, 77%): mp 59-60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 3H), 1.16 (s, 3H), 1.21 (m, 2H), 1.23 (s, 3H), 1.40 (m, 1H), 1.71 (m, 2H), 1.93 (m, 1H), 2.18 (m, 1H), 3.28 (s, 2H), 3.10 (s, SH), 7.19 (d,, *J* = 7.69 Hz, 1H), 7.45 (dd, J = 8.05 Hz, J = 7.68 Hz, 1H), 7.64 (dd, *J* = 8.05 Hz, J = 8.06 Hz, 1H), 8.12 (d, *J* = 8.06 Hz, 1H), 8.21 (m, 1H), 8.49 (br, NH), 8.78 (m, 1H), 9.14 (s, 1H); ^{13}C NMR δ 18.08 (q), 24.35 (t), 27.44 (q), 28.94 (q), 33.65 (t), 40.21 (t), 45.42 (s), 47.97, (t), 50.76 (d), 54.59 (s), 62.39 (s), 110.98 (d), 121.37 (d), 123.36 (d), 129.96 (s), 135.02 (d), 138.16 (d), 148.05 (d), 149.25 (s), 152.45 (d), 160.50 (s), 163.70 (s); HRMS calcd 381.187, found 381.187. Anal. Calcd for $C_{22}H_{27}N_3SO$: C, 69.26; H, 7.13; N, 11.01; S, 8.40. Found: C, 68.74; H, 7.25; N, 10.71; S, 8.34.

1-methyl-3-{[(6-{[(1R,2R)-1,3,3-trimethyl-2-sulfanylbicyclo[2.2.1]hept-2-yl]methyl}-2-pyridinyl)amino]carbonyl}pyridinium perchlorate 7.11a.

The thiofenchone derivative **7.10** (0.85 g, 2.2 mmol) was dissolved in 25 mL of acetonitrile, $LiClO_4$ (0.51 g, 4.8 mmol) and methyliodide (0.7 g, 4.8 mmol) were added. Stirring was continued overnight at 50°C. After removal of the solvent the product was purified by means of column chromatography (silica; acetonitrile / dichloromethane (1:2)) affording **7.11a** as a white solid (1.0 g, 2.1 mmol, 95 %); ^{1}H NMR (300 MHz, CD_3OD) δ 0.41 (s, 3H), 0.74 (m, 1H), 0.77 (s, 3H), 0.81 (s, 3H), 1.01 (m, 1H), 1.22 (m, 1H), 1.34 (m, 1H), 1.63 (m, 1H), 1.80 (m, 1H), 2.95 (dd, J = 16.8 Hz, J = 26.0 Hz, 2H), 4.10 (s, 3H), 6.84 (d, *J* = 7.69 Hz, 1H), 7.31

(t, J = 7.68 Hz, 1H), 7.60 (d, *J* = 8.06 Hz, 1H), 7.81 (d, *J* = 6.23 Hz, 1H), 8.64 (m, 2H), 9.07 (s, 1H); ^{13}C NMR (CD_3CN) δ 16.79, 23.41, 26.38, 27.84, 32.35, 39.01, 44.65, 46.79, 47.83, 49.83, 53.54, 61.27, 111.09, 121.54, 127.08, 133.56, 137.74, 142.87, 143.08, 144.31, 146.33, 147.98, 160.25; HRMS calcd 495.159, no proper HRMS could be obtained but CI(NH_3) gave a molecular ion at m/e 396. Anal. Calcd for $C_{23}H_{30}N_3SO_5Cl$: C, 55.69; H, 6.10; N, 8.47; S, 6.46. Found: C, 55.45; H, 6.05; N, 8.54; S, 6.41.

1-benzyl-3-{[(6-{[(1*R*,2*R*)-1,3,3-trimethyl-2-sulfanylbicyclo[2.2.1]hept-2-yl]methyl}-2-pyridinyl)amino]carbonyl}pyridinium bromide 7.11b.

The thiofenchone derivative **7.10** (0.21 g, 0.55 mmol) was dissolved in 50 mL of dichloromethane and benzylbromide (0.43 g, 2.5 mmol) was added. After stirring for 18h the solution was concentrated in vacuo and the solid was washed with diethyl ether twice and recrystallized from 2-propanol affording **7.11b** as a white solid (0.26 g, 0.47 mmol, 85 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71 (s, 3H), 1.04 (m, 1H), 1.08 (s, 3H), 1.14 (s, 3H), 1.31 (m, 1H), 1.55 (m, 1H), 1.65 (m, 1H), 1.80 (m, 1H), 1.88 (m, 1H), 2.13 (m, 1H), 3.21 (s, 2H), 4.73 (s, SH), 6.15 (s, 2H), 7.00 (d, *J* = 7.3 Hz, 1H), 7.36 (m, 3H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.58 (m, 2H), 7.77 (d, *J* = 8.1 Hz, 1H), 8.00 (m, 1H), 8.89 (d, *J* = 8.1 Hz, 1H), 9.32 (d, *J* = 5.9 Hz, 1H), 10.17 (br, NH); ^{13}C NMR δ 18.29, 24.61, 25.27, 27.82, 29.32, 33.58, 10.41, 45.84, 48.09, 50.93, 54.64, 62.28, 64.65, 121.97, 127.51, 129.66, 129.72, 130.15, 131.95, 134.73, 138.13, 144.49, 145.29, 145.63, 149.18, 159.99; HRMS calcd 551.161, no proper HRMS could be obtained but CI(NH_3) gave a molecular ion at m/e 472. Anal. Calcd for $C_{29}H_{34}N_3SOBr$: C, 63.04; H, 6.20; N, 7.60; S, 5.80; Br, 14.46. Found: C, 63.15; H, 6.25; N, 7.70; S, 5.75.

1-methyl-*N*-(6-{[(1*R*,2*R*)-1,3,3-trimethyl-2-sulfanylbicyclo[2.2.1]hept-2-yl]methyl}-2-pyridinyl)-1,4-dihydro-3-pyridinecarboxamide 7.5a.

To a stirred solution of pyridinium adduct **7.11a** (0.20 g, 0.39 mmol) in 150 mL of methanol and 15 mL of a phosphate buffer (Merck Puffer-titrisol pH=7.00) was added $Na_2S_2O_4$ (0.44 g, 2.5 mmol) in 25 mL of water. The mixture was stirred for 5 min and then extracted with dichloromethane twice. The combined organic layers were dried over Na_2SO_4 and after concentration the product was flushed over a short column of silica with dichloromethane/acetonitrile (10:1). Product **7.5a** was obtained as a yellow product that decomposed upon standing (0.15 g, 0.37 mmol, 96 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.14 (m, 1H), 1.17 (s, 3H), 1.21 (m, 1H), 1.24 (s, 3H), 1.40 (m, 1H), 1.65 (m, 1H), 1.73 (m, 1H), 1.90 (m, 1H), 2.16 (m, 1H), 2.98 (s, 3H), 3.24 (s, 2H), 3.30 (s, 2H), 3.73 (s, SH), 4.80 (m, 1H), 5.70 (d, *J* = 8.1 Hz, 1H), 6.98 (d, J = 7.7 Hz, 1H), 7.10 (s, 1H), 7.44 (br, NH), 7.53 (t, *J* = 8.1 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 1H). No HRMS or elemental analysis could be obtained because of the instability of the product.

1-benzyl-*N*-(6-{[(1*R*,2*R*)-1,3,3-trimethyl-2-sulfanylbicyclo[2.2.1]hept-2-yl]methyl}-2-pyridinyl)-1,4-dihydro-3-pyridinecarboxamide 7.5b.

To a stirred solution of **7.11b** (0.25 g, 0.45 mmol) in 100 mL of methanol and 25 mL of a phosphate buffer (Merck Puffer-titrisol pH=7.00) was added $Na_2S_2O_4$ (0.53 g, 3.0 mmol) in 10 mL of water. The mixture was stirred for 5 min and extracted twice with dichloromethane. The organic layers were dried of Na_2SO_4 and concentrated. Column chromatography (silica; dichloromethane / acetonitrile (10:1)) afforded **7.5b** as a yellow viscous oil (0.13 g, 0.27 mmol, 60 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1.12 (s, 3H), 1.19 (s, 3H), 1.35 (m, 2H), 1.60 (m, 3H), 1.85 (m, 1H), 2.11 (m, 1H), 3.19 (s, 2H), 3.29 (s, 2H), 3.65 (s, SH), 4.28 (s, 2H), 4.76 (m, 1H), 5.72 (d, J = 6.1 Hz, 1H), 6.93 (d, J = 7.3 Hz, 1H), 7.2 (m, 6H), 7.48 (dd, J = 7.3 Hz, J = 8.1 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H). No HRMS or elemental analysis could be obtained because of the instability of the product

***N*-(6-{[(1*R*,2*S*)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methyl}-2-pyridinyl)nicotinamide 7.12**

To a stirred solution of **7.9** (1.5 g, 7.0 mmol) in 200 mL of THF at –70°C was added KDA (0.25 M solution in THF, 60 mL, 15 mmol) and stirring continued for 10 min before a solution of (*R*)-camphor (1.1 g, 7.2 mmol) in 25 mL of THF was added. The mixture was stirred at –70°C for 1h and at RT overnight. After addition of 2N NH_4Cl the mixture was extracted with ethyl acetate twice. The combined organic layers were washed with brine and dried over Na_2SO_4. The product was purified by means of column chromatography (silica, hexane/ethyl acetate 1:1) yielding a white solid, which was recrystallized from dichloromethane/hexane (1.1 g, 3.0 mmol, 43%): mp 130-131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.40 (s, 3H), 0.81 (s, 3H), 1.06 (s, 3H), 1.07 (m, 1H), 1.41 (m, 3H), 1.69 (m, 2H), 2.01 (m, 1H), 2.93 (s, 2H), 5.44 (br, OH), 7.02 (d, *J* = 7.32 Hz, 1H), 7.44 (dd, J = 7.69 Hz, J = 8.06 Hz, 1H), 7.71 (dd, *J* = 7.69 Hz, J = 8.06 Hz, 1H), 8.17 (m, 2H), 8.22 (d, *J* = 8.42 Hz, 1H), 8.64 (br, NH), 8.78 (d, J = 3.36 Hz, 1H), 9.13 (s, 1H); ^{13}C NMR δ 10.98 (q), 20.77 (q), 21.13 (q), 26.92 (t), 30.48 (t), 44.69 (t), 44.98 (t), 46.71, (d), 49.27 (s), 52.25 (s), 81.15 (s), 111.98 (d), 120.77 (d), 123.27 (d), 129.93 (s), 135.09 (d), 138.04 (d), 148.30 (d), 149.81 (s), 152.42 (d), 158.75 (s), 164.09 (s); HRMS calcd 365.211, found 365.210. Anal. Calcd for $C_{22}H_{27}N_3O_2$: C, 72.30; H, 7.45; N, 11.50. Found: C, 72.05; H, 7.49; N, 11.37.

1-methyl-3-{[(6-{[(1*R*,2*S*)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methyl}-2-pyridinyl)amino]carbonyl}pyridinium iodide 7.13

To a stirred solution of **7.12** (0.50 g, 1.4 mmol) in 10 mL of acetonitrile was added methyliodide (0.20 g, 1.4 mmol) and the mixture was stirred overnight at 50 °C. The solvent was evaporated and the product was recrystallized from 2-propanol yielding a white solid

(0.68 g, 1.3 mmol, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.34 (s, 3H), 0.67 (s, 3H), 0.90 (s, 3H), 0.96 (m, 1H), 1.17 (m, 1H), 1.34 (m, 2H), 1.58 (m, 2H), 1.82 (m, 1H), 2.65 (dd, J = 14.32 Hz, J = 14.32 Hz, 2H), 4.54 (s, 3H), 6.86 (br, OH), 6.85 (d, J = 7.32 Hz, 1H), 7.60 (dd, J = 7.68 Hz, J = 8.06 Hz, 1H), 7.94 (d, J = 8.06 Hz, 1H), 8.08 (m, 1H), 8.80 (d, J = 8.42 Hz, 1H), 9.45 (d, J = 6.23 Hz, 1H), 10.13 (s, 1H), 10.6 (br, NH); HRMS calcd 507.138, , no proper HRMS could be obtained but CI(NH_3) gave a molecular ion at m/e 366 (-I, -CH_3). Anal. Calcd for $C_{23}H_{30}N_3O_2I$: C, 54.44; H, 5.96; N, 8.28. Found: C, 54.24; H, 6.01; N, 8.24.

1-methyl-*N*-(6-{[(1*R*,2*S*)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methyl}-2-pyridinyl)-1,4-dihydro-3-pyridinecarboxamide 7.14

To a stirred solution of **7.13** (0.66 g, 1.3 mmol) in 200 mL of methanol was added lithium perchlorate (0.14 g, 1.3 mmol). The mixture was stirred for 1 h and 50 mL of a phosphate buffer(Merck Puffer-titrisol pH=7.00) was added. $Na_2S_2O_4$ (1.5 g, 8.6 mmol) in 10 mL of water was added with vigorous stirring. After stirring for 30 min 200 mL of water was added and the mixture was extracted with dichloromethane twice. The combined organic layers were dried over Na_2SO_4 and after concentration in vacuo the product was flushed over a column of aluminum oxide with dichloromethane. A unstable yellow oil was obtained that was used as such for the reduction reactions (0.46 g, 0.9 mmol, 70 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48 (s, 3H), 0.75 (s, 3H), 1.00 (m, 1H), 1.03 (s, 3H), 1.29 (m, 1H), 1.38 (m, 2H), 1.63 (m, 2H), 1.94 (m, 2H), 2.82 (s, 2H), 2.91 (s, 3H), 3.20 (s, 2H), 4.74 (m, 1H), 5.64 (d, *J* = 8.1 Hz, 1H), 5.8 (br, OH), 6.82 (d, J = 7.7 Hz, 1H), 7.01 (s, 1H), 7.36 (br, NH), 7.55 (t, *J* = 8.1 Hz, 1H), 8.10 (d, *J* = 8.1 Hz, 1H). No HRMS or elemental analysis could be obtained because of the instability of the product.

General Procedure for the reduction of ethyl phenylglyoxylate.

To a stirred solution of ethyl phenylglyoxylate (1.0 mmol) in 5 mL of acetonitrile was added the dihydropyridine adduct (1.2 mmol) followed by the addition of a zinc or magnesium perchlorate (1.2 mmol). The mixture was stirred in the dark for the given time and samples were taken to determine the conversion by means of GC analysis (HP-1; 30m x 0.25 mm x 0.25μm; flow He 1.3 mL/min; T(oven) 100°C 2 min, 20°C/min↑; T(det/inj) 350 °C; split ratio 150:1; Vinj = 0.2 μL. T_R of ketone 5.91 min, T_R of alcohol 5.75 min) After the reaction was complete the mixture was quenched with water and extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by means of column chromatography (silica; ether / hexane (1:3)) affording the alcohol. The enantiomeric excess was determined by means of HPLC (OB-H; hep:IPA (95:5); flow: 0.5 ml/min; T_R of (S)-**7.4** 22.7 min and (R)-**7.4** 26.44 min)

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CHAPTER 8

Phenanthroline and Bipyridine Diols.

Abstract: Neocuproine **8.1** and 6,6'-dimethyl-2,2'-bipyridine **8.6** were converted to chiral and achiral tetradentate phenanthroline diols **8.2** and bipyridine diols **8.7** making use of base-induced addition to (a)chiral ketones. Reactions with benzophenone and adamantanone proceeded smoothly although small amounts of mono adducts **8.3** and **8.8** were also formed. Functionalization of neocuproine **8.1** with (*R*)-camphor failed under the standard conditions. However, conversion of the lithiospecies **8.4** to the cerium chloride species **8.5** and subsequent reaction with (*R*)-camphor led to the phenanthroline diols **8.2e**. Complexes of the diols **8.2** and **8.7** with zinc, copper, and cobalt were prepared. X-ray analysis of the zinc complex **8.9** of diol **8.7a** showed a five coordinated zinc ion that is firmly embedded in the ligand. X-ray analysis of the copper complex **8.10** of diol **8.7a** unexpectedly revealed this to be an acetate bridged di-copper species. This copper complex is formed upon recrystallization from ethyl acetate. The initial complex appears to hydrolyze the ethyl acetate to provide the bridging acetate found in the di-copper complex **8.10**.

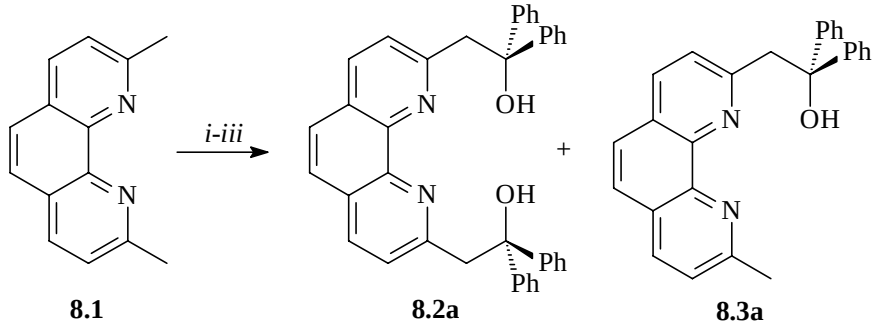
8.1 Introduction.

Both 1,10-phenanthrolines and 2,2'-bipyridines are attractive building blocks in organic chemistry and they are often incorporated into hosts and ligand systems. These moieties provide two aromatic nitrogen atoms whose unshared electron pairs are placed so that they act cooperatively in binding cations. Therefore these ligands are strongly chelating for a variety of metal ions.[1] Metal-ion complexes with functionalized 1,10-phenanthrolines have been used as catalyst for the enantioselective hydrolysis of *N*-protected amino acid esters,[2] in the oxidative cleavage of DNA,[3] in palladium catalyzed allylic substitution[4] and in enantioselective reduction of acetophenone.[5,6] Bipyridines and derivatives thereof are also well know for their complexation with metals.[7] Functionalized 2,2'-bipyridines have been used in enantioselective alkylation of aldehydes,[8,9] in enantioselective hydrosilation of ketones,[10] in asymmetric allylation,[11] in cyclopropanation of styrene,[12] in palladium catalyzed allylic substitution,[13] and as herbicides.[14] These building blocks are also frequently used for the synthesis of (mixed) crown ethers,[15] catenates and catenands,[16] and for the formation of macromolecular structures and grids.[17]

Functionalization of these phenanthroline and bipyridine moieties to phenanthroline diols and bipyridine diols could afford interesting tetradentate ligands for metal complexation. Making use of our approach used for the synthesis of pyridine diols **2.1** and pyridine dithiols **3.1** functionalization of 2,9-dimethyl-1,10-phenathroline (neocuproine) and 6,6'-dimethyl-2,2'-bipyridine at the 2,9-position and the 6,6-position respectively should afford the corresponding diols.

8.2 Synthesis of Phenanthroline Diols.

When neocuproine **8.1** was deprotonated at the methyl groups with 2.5 equiv. of LDA at –80°C and subsequently quenched with benzophenone the phenanthroline diol **8.2a** was obtained in 55% yield together with 15% of the mono-adduct **8.3a** (Scheme 8.1).

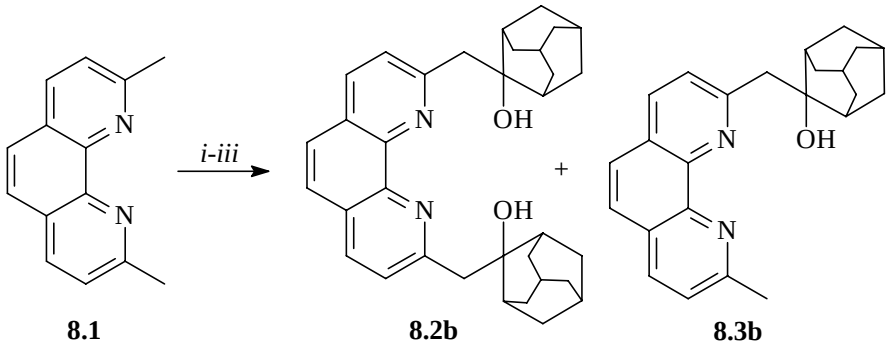


8.1 **8.2a** **8.3a**

Scheme 8.1 *Reagents and conditions*: *i*, LDA, -80°C; *ii* benzophenone; *iii* 2N NH_4Cl.

The bis-adduct was separated from the mono-adduct by washing with hot ethanol. The bis-adduct was purified by recrystallization from chloroform/acetonitrile/hexane. Lowering the excess of LDA gave rise to an increase in formation of the mono-adduct. Deprotonation of neocuproine with *n*-butyllithium gave rise to undefined side products.

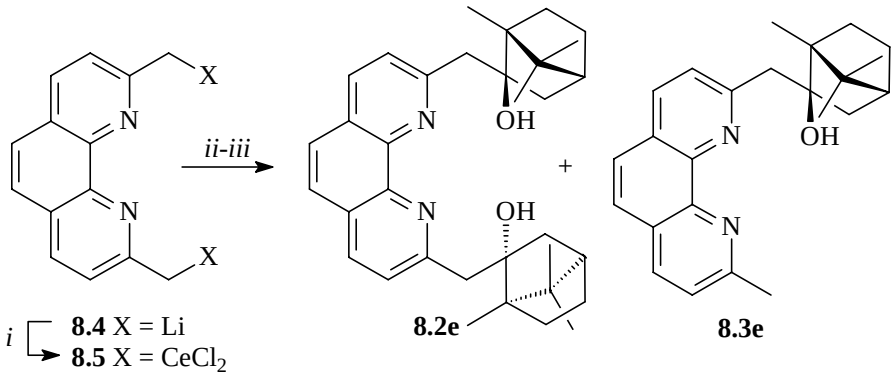
When adamantanone instead of benzophenone was used for the functionalization of neocuproine **8.1** the bis-adduct **8.2b** was obtained in 49% yield (Scheme 8.2). The mono-adduct **8.3b** was separated upon recrystallization from ethyl acetate.



8.1 **8.2b** **8.3b**

Scheme 8.2 *Reagents and conditions*: *i,* LDA, -80°C; *ii* adamantanone; *iii* 2N NH_4Cl.

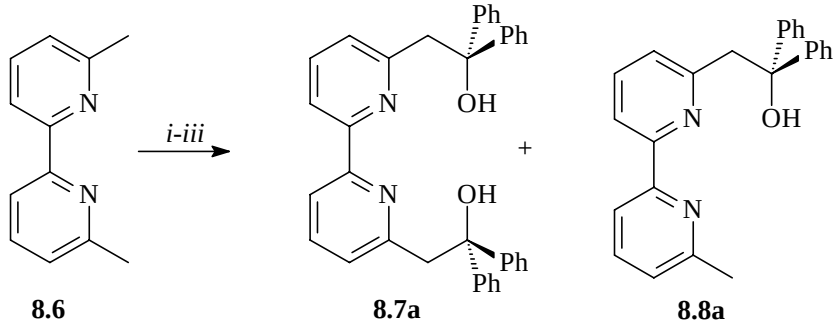
The lower yield related to the benzophenone adduct is probably due to the relative lower reactivity of the carbonyl functionality of adamantanone relative to the carbonyl group of benzophenone. When (*R*)-camphor, which is even less reactive than adamantanone and easily undergoes enolization, was allowed to react with the bislithiated neocuproine **8.1** formation of the desired diol **8.2e** or the mono-adduct **8.3e** was not observed. At –80°C no reaction at all occurs. However, when the temperature was raised to –50°C decolorization occurred indicating the disappearance of the dilithio adduct. Workup afforded only starting material indicating that at –50°C the (*R*)-camphor is enolized by the dilithio species rather than attacked at the carbonyl functionality. In order to effect addition to (*R*)-camphor the more oxaphilic and less basic alkyl cerium reagent was generated.[18] The dilithio species **8.4** was converted to the $CeCl_2$ species **8.5** by addition of $CeCl_3$·THF after lithiation. When the dilithiated neocuproine **8.4** was stirred with $CeCl_3$·THF for 1 hour and quenched with (*R*)-camphor the chiral phenanthroline diol **8.2e** was formed in 65% yield (Scheme 8.3). The small amount of the mono-adduct **8.3e** that was formed could be removed by crystallization from ethyl acetate. Concentration of the mother liquor gave the mono-adduct **8.3e**.



Scheme 8.3 *Reagents and conditions*: *i*, $CeCl_3$·THF, -80°C; *ii* (*R*)-camphor; *iii* 2N NH_4Cl.

8.3 Synthesis of Bipyridine Diols.

Functionalization of 6,6'-dimethyl-2,2'-bipyridine **8.6** was achieved according to the procedure for neocuproine. Lithiation of 6,6'-dimethyl-2,2'-bipyridine **8.6** with 2.5 equiv. of LDA and subsequent addition of benzophenone afforded the bipyridine diol **8.7a** in 49% yield along with 29% of the mono-adduct **8.8a** (Scheme 8.4). The mono and bis-adduct could be separated based on the lower solubility of the bis-adduct in methanol.



Scheme 8.4 *Reagents and conditions*: *i*, LDA, -80°C; *ii* benzophenone; *iii* 2N NH_4Cl.

8.4 Complexations with Metals.

Ligands with a phenanthroline or bipyridine moiety are usually strong metal chelating and the phenanthroline and bipyridine based tetradentate diols were also found to form stable complexes with zinc and copper. When zinc perchlorate heptahydrate was added to a suspension of phenanthroline diol **8.2e** in a mixture of $CD_3CN/CDCl_3$ (9:1) a complex was formed. A large downfield shift of 150 Hz (300 MHz) for the aromatic protons (referring to the free ligand in the same solvent mixture) was observed indicating complexation of the phenanthroline moiety. The benzylic protons gave a set of 4 signals which indicates that these protons are diastereotopic and that the complex has a locked conformation on the NMR scale.

Furthermore a signal for the hydroxyl groups can be found at δ 5.40 which means that the zinc has not deprotonated the alcohol functionalities.

After addition of zinc perchlorate heptahydrate to a suspension of the bipyridyl diol **8.7a** in a mixture of CD_3CN and $CDCl_3$ (9/1) the material slowly dissolved and the complex **8.9** was formed. Again complexation gave rise to a downfield shift of the pyridine protons. Furthermore the benzylic protons are shifted 120 Hz downfield (referring to the free ligand). The benzylic protons give rise to a singlet, which could indicate some flexibility in the complex as a consequence of the flexibility of the bipyridine bond. Also a signal for the hydroxyl groups is observed, indication that deprotonation did not take place. More structural information of the complex was obtained from the X-ray structure of the complex **8.9**. Crystals for X-ray were grown from ethyl acetate/acetonitrile and isothermal distillation of hexane into the solution.

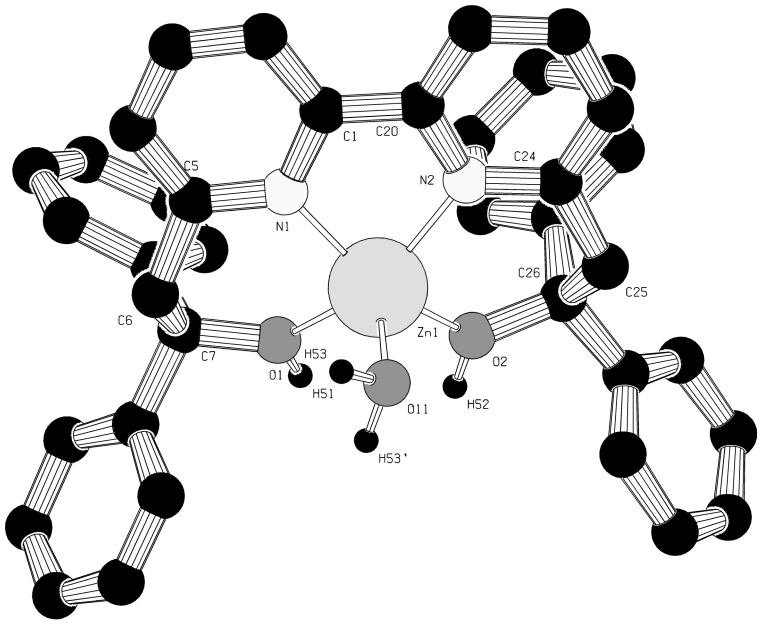


Figure 8.1 *X-ray structure of **8.9** without the perchlorate counter ions.*

Although an X-ray structure determination was thwarted by persistent weak scattering crystals and also broad reflections, ultimately a data set was gathered from which a successful structure determination was obtained (Figure 8.1). The crystal structure shows a pentacoordinated zinc atom in a square pyramidal surrounding: The two hydroxyl groups, the two nitrogen groups and an additional water molecule are involved in the binding of the zinc in a square pyrimidal fashion. The zinc is situated in the middle of the molecule, which roughly has a symmetry axis through the zinc, the water molecule and the bipyridine bond. The bipyridine bridge moiety is almost flat and the hydroxyl groups are pointing towards the zinc.

Complexes with copper were also easily formed. Addition of Cu(I)triflate.benzene complex to 2,2'-bipyridyl diol **8.7a** in acetonitrile under argon immediately afforded a red solution which turns blue after a few seconds of stirring indicating that the Cu(I) is converted to a more stable Cu(II). This complex is also supported by the observation of a paramagnetic nucleus (by NMR) in the solution. Since no elemental Cu is observed it is most probably that the Cu(I) is oxidized by the ligand. Complexations of $Cu(acac)_2$ with 2,2'-bypyridine diol **8.7a** in acetonitrile were more successful and a blue crystalline precipitate was formed. The ^{1}H NMR of this complex in chloroform showed a paramagnetic nucleus and complexation with the ligand. Whether the alcohol functionalities are deprotonated or not is unclear from the ^{1}H NMR spectra. Suitable crystals for X-ray diffraction were grown by recrystallization from hot ethyl acetate. Surprisingly X-ray analysis showed a di-copper complex **8.10** in which the copper ions are bridged by acetate groups and the hydroxylates. The asymmetric unit of the crystals consisted of two di-Cu complexes and four heavily disordered acetate molecules (Figure 8.2).

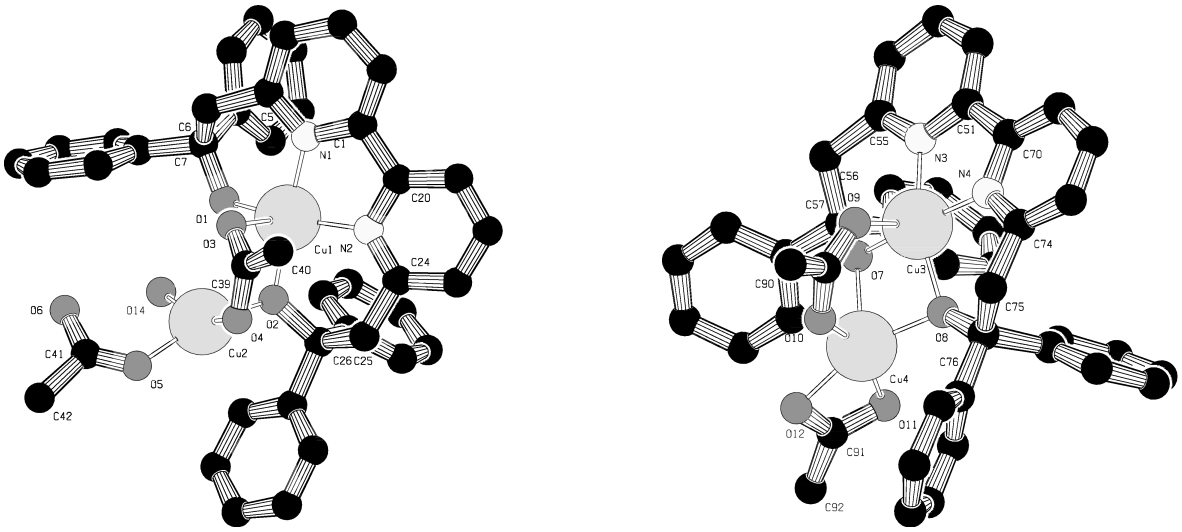


Figure 8.2 *X-ray structure of residues 1(left) and 2 of complex **8.10.***

In the first residue (left) the one copper ion is symmetrically bond to the bipyridine nitrogens, an acetate oxygen and the hydroxylates of the ligand attaining a square pyrimidal surrounding (Cu(1)…N(1) 1.954 Å; Cu(1)…N(2) 2.000 Å; Cu(1)…O(3) 2.342 Å; Cu(1)…O(1) 1.913 Å; Cu(1)…O(2) 1.913 Å). The second copper ion also coordinates to one of the hydroxylates and is bridged to the other copper ions through the acetate molecule. A second acetate molecule is coordinated to this copper. The fourth coordination site of this copper is filled with a water molecule. The distance between the two copper ions Cu(1) and Cu(2) is 3.151 Å, which is comparable to the distances found for other di-copper complexes.[19] The ligand backbone is slightly twisted; a torsion angle of -5.1° is observed. The second residue (right) embeds like the first residue two copper ions. These ions are bridged

by both hydroxylates and by a acetate molecule. The distance between the two copper ions in this structure is somewhat shorter (Cu(3)…Cu(4) 2.8861 Å). The first copper ion is embedded in the ligand and is square pyrimidal coordinated. The second copper ion coordinates to both hydroxylate groups (Cu(3)…O(7) 2.225 Å; Cu(3)…O(8) 1.932 Å). No coordination of water is found in this residue. The bipyridine backbone is nearly flat, a torsion angle of -4.2 ° being observed.

Although the synthesis of this complex was started with free ligand and $Cu(acac)_2$ the inclusion of the acetate molecules in the X-ray structure can be explained by the hydrolysis of ethyl acetate upon heating. Probably water present in the complex gives rise to the hydrolysis.

8.5 Conclusions.

Phenanthroline diols **8.2** and bipyridine diols **8.7** have been prepared using the method described in Chapter 2 for the synthesis of pyridine diols. Monoadduct **8.3** and **8.8** respectively were formed as a side product but can easily be removed. Although nucleophilicity of the dilithiated neocuproine and 6,6'-dimethyl-1,1'-bipyridine is less than lithiated 2,6-lutidine, reactions with benzophenone and adamantanone occur smoothly. Reaction with (*R*)-camphor however was thwarted by the lower nucleophilicity. Conversion of the dilithiospecies **8.4** to the cerium chloride adduct **8.5** enhanced the reactivity towards (*R*)-camphor and the camphor based diol **8.2e** could be isolated. Complexations of these diols with zinc afforded stable complexes. Characterization of one of these complexes by X-ray analysis showed a firmly embedded five coordinated zinc ion. Complexations of copper with the bipyridine diol **8.7a** afforded a di-copper complex **8.10** that is probably formed after hydrolysis of ethyl acetate by the complex.

8.6 Experimental Section.

General Remarks: See Chapter 2. Anhydrous neocuproine was obtained by recrystallization from benzene. $CeCl_3 \cdot 7H_2O$ was dried according to the literature.[21]

2-[9-(2-hydroxy-2,2-diphenylethyl)[1,10]phenanthrolin-2-yl]-1,1-diphenyl-1-ethanol 8.2a.

To a stirred solution of neocuproine **8.1**[20] (0.25 g, 1.2 mmol) in 50 mL of THF at –80°C was added LDA (2.0 M solution in THF/*n*-heptane, 1.5 mL, 3.0 mmol). After stirring for 1h a solution of benzophenone (0.54 g, 3.0 mmol) in 5 mL of THF was added. Stirring remained overnight allowing the mixture to reach room temperature. The solution was quenched with 2N NH_4Cl and chloroform/acetonitrile (1:1) 100 mL was added. The solution was sonicated for 1 h and the layers were separated. The aqueous layer was washed with chloroform twice.

The combined organic layers were dried over Na_2SO_4. After evaporation of the solvent the solid was washed with hot ethanol yielding the bis-adduct, which was crystallized from chloroform/acetonitrile/hexane to afford the bis-adduct **8.2a** as a hydrate (0.47 g, 0.8 mmol, 55%): mp 208-209 °C; ^{1}H NMR (300 MHz, CD_3CN): δ 1.53 (br, H_2O), 4.00 (s, 4H), 7.07 (m, 4H), 7.19 (m, 10H), 7.29 (d, *J* = 8.05 Hz, 2H), 7.57 (m, 8H), 7.95 (d, *J* = 8.05 Hz, 2H). δ; HRMS calcd 572.246; no proper HRMS could be obtained, CI(NH_3) gave a molecular ion at *m/e* 573. Anal. Calcd for $C_{80}H_{66}N_4O_5$: C, 82.59; H, 5.72; N, 4.82. Found C, 82.94; H, 5.84; N, 4.81.

2-({9-[(2-hydroxy-2-adamantyl)methyl][1,10]phenanthrolin-2-yl}methyl)-2-adamantanol 8.2b.

A solution of neocuproine **8.1** (0.30g, 1.44 mmol) in 50 mL of THF was cooled to –80°C and LDA (2.0 M solution in THF/*n*-heptane, 1.8 mL, 3.6 mmol) was slowly added. After stirring for 1h adamantanone (0.54 g, 3.6 mmol) in 5 mL of THF was added. The mixture was quenched with 2N NH_4Cl and extracted with dichloromethane twice. The combined organic layers were washed with brine and dried over Na_2SO_4. The bis-adduct **8.2b** was recrystallized from ethyl acetate to afford colorless needles (0.36 g, 0.71 mmol, 49%): mp 221-223 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (m, 4H), 1.71 (m, 10H), 1.78 (m, 4H), 1.90 (m, 2H), 2.01 (m, 4H), 2.43 (m, 4H), 3.48 (s, 4H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.73 (s, 2H), 8.16 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR: δ 27.42 (d), 27.50 (d), 32.75 (t), 34.72 (t), 37.28 (d), 38.51 (t), 44.56 (t), 75.42 (s), 124.56 (d), 125.50 (d), 126.94 (s), 136.27 (d), 160.40 (s); HRMS calcd 508.309; found 508.309. Anal. Calcd for $C_{34}H_{40}N_2O_2$: C, 80.28; H, 7.93; N, 5.51. Found C, 80.28; H, 7.77; N 5.46.

(1*R*,2*S*)-2-[(9-{[(1*R*,2*S*)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methyl}-[1,10]phenanthrolin-2-yl)methyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 8.2e.

A solution of $CeCl_3$[21] (1.61 g, 6.5 mmol) in 150 mL of THF was sonicated overnight and cooled to –80°C. Subsequently a previous prepared solution of lithiated neocuproine **8.4** (0.03N solution in THF, 1.6 mmol, 53 mL) was slowly added. Stirring remained at –80°C for 1h after which (*R*)-camphor (0.87 g, 5.7 mmol) in 5 mL of THF was added. Stirring continued for 3h allowing the mixture to reach –10°C, subsequently the mixture was quenched with 2N NH_4Cl and extracted with dichloromethane twice. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure the product was flushed over a short column (silica, ethyl acetate/hexane (1:3)). The obtained solid was recrystallized from ethyl acetate affording **8.2e** as a white solid (0.53 g, 1.0 mmol, 65%): mp 199-201 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.51 (s, 6H), 0.77 (s, 6H), 1.09 (m, 2H), 1.17 (s, 6H), 1.42 (m, 6H), 1.66 (m, 4H), 2.35 (m, 2H), 3.28 (m, 4H), 6.6 (br, 2OH), 7.45 (d, *J* = 8.05 Hz, 2H), 7.67 (s, 2H), 8.11 (d, *J* = 8.05 Hz, 2H); ^{13}C NMR: δ

11.21 (q), 21.05 (q), 21.58 (q), 27.21 (t), 30.92 (t), 45.13 (d), 45.84 (t), 47.28 (t), 49.40 (s), 52.46 (s), 81.05 (s), 124.46 (d), 125.54 (d), 126.95 (s), 129.12 (s), 136.35 (d), 161.31 (s); HRMS calcd 512.340; found 512.340. Anal. Calcd for $C_{34}H_{44}N_2O_2$: C, 79.65; H, 8.65; N, 5.46. Found C, 79.24; H, 8.79; N, 5.44.

2-[3'-(2-hydroxy-2,2-diphenylethyl)[2,2'-bipyridyl]-6-yl]-1,1-diphenyl-1-ethanol 8.7a.
The 2,2'-bipyridyl **8.6**[22] (0.16 g, 0.87 mmol) was dissolved in 25 mL of THF and lithiated at –80°C with LDA (2.0 M solution in THF/*n*-heptane, 1.1 mL, 2.2 mmol). After stirring for 1h at –80°C a solution of benzophenone (0.40 g, 2.2 mmol) in 5 mL of THF was added. The mixture was allowed to reach ambient temperature in 3 h and was quenched with 2N NH_4Cl. The mixture was extracted with dichloromethane twice and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent the solid was washed with methanol and recrystallized from chloroform/hexane to afford the bis-adduct **8.7a** as hydrate (0.23 g, 0.43 mmol, 49 %): mp > 230 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (br, H_2O), 3.78 (s, 4H), 7.04 (m, 2H), 7.11 (m, 4H), 7.20 (m, 8H), 7.40 (m, 8H), 7.52 (br, 2OH), 7.60 (t, *J* = 7.69 Hz, 2H), 7.86 (d, *J* = 8.06 Hz, 2H). ^{1}H NMR (300 MHz, $CD_3CN/CDCl_3$): δ 3.53 (s, 4H), 6.82 (m, 4H), 6.94 (m, 8H), 7.00 (d, *J* = 7.32 Hz, 2H), 7.22 (m, 8H), 7.50 (m, 4H); ^{13}C NMR: δ 46.92 (t), 78.32 (s), 118.91 (d), 124.91 (d), 128.98 (d), 126.48 (d), 127.90 (d), 138.07 (d), 146.94 (s), 153.77 (s), 158.57 (s); HRMS calcd 548.246; found 548.246 Anal. Calcd for $C_{38}H_{34}N_2O_3$: C, 80.54; H, 6.05; N, 4.94. Found C, 80.85; H, 5.83; N 4.99.
The methanolic solution was concentrated and the solid was recrystallized from ethanol affording the mono-adduct **8.8a** as a white solid. (0.09 g, 0.25 mmol, 29%): mp 194-195 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.55 (s, 3H), 3.74 (s, 2H), 7.00 (d, *J* = 7.7 Hz, 1H), 7.11 (m, 3H), 7.19 (m, 4H), 7.43 (m, 4H), 7.62 (m, 2H), 7.87 (br, OH), 7.93 (d, *J* = 8.1 Hz, 1H), 8.14 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR: δ 24.52 (q), 46.87 (t), 78.35 (s), 117.85 (d), 119.07 (d), 123.39 (d), 124.49 (d), 126.03 (d), 126.40 (d), 127.87 (d), 137.18 (d), 137.81 (d), 147.05 (s), 154.90 (s), 157.92 (s), 158.31 (s); HRMS calcd 366.173; found 366.173 Anal. Calcd for $C_{25}H_{22}N_2O$: C, 81.94; H, 6.05; N, 7.64. Found C, 81.44; H, 6.07; N, 7.46.

Zinc complex of 8.2e
The diol **8.2e** (30 mg, 59 μmol) was suspended in 1 mL of CD_3CN and zinc perchlorate heptahydrate (22 mg, 59 μmol) was added upon which the solution became clear. ^{1}H NMR showed quantitative conversion to the complex. The solvent was evaporated and the solid was crystallized from chloroform/acetone (1:1) with isothermal distillation of hexane into the solution affording **8.10** as colorless crystals (37 mg, 47 μmol, 80%): ^{1}H NMR (300 MHz, $CD_3CN/CDCl_3$): δ 0.37 (s, 6H), .28 (s, 6H), .78 (s, 6H), 0.93 (m, 2H), 1.28 (m, 6H), 1.54 (m,

4H), 1.94 (m, 2H), 2.2 (br, H_2O), 3.30 (d, *J* = 16.48 Hz, 2H), 3.43 (d, *J* = 16.48 Hz, 2H), 5.40 (s, 2OH), 7.79 (d, *J* = 8.43 Hz, 2H), 7.89 (s, 2H), 8.50 (d, *J* = 8.43 Hz, 2H). ^{13}C NMR: δ 9.92 (q), 19.31 (q), 20.09 (q), 24.96 (t), 30.20 (t), 43.42 (t), 43.76 (d), 45.61 (s), 48.72 (t), 52.66 (s), 88.14 (s), 125.73 (d), 126.91 (s), 127.19 (d), 133.05 (s), 140.88 (d), 160.01 (s); HRMS calcd 774.166; no proper HRMS could be obtained. Anal. Calcd for $C_{34}H_{44}N_2O_{10}ZnCl_2$: C, 52.56; H, 5.71; N, 3.61; Zn, 8.41. Found C, 52.46; H, 5.64; N, 3.63; Zn, 8.54.

Zinc complex of 8.7a

To a suspension of the ligand **8.7a** (48 mg, 88 μmol) in 1 mL of CD_3CN + 0.1 mL $CDCl_3$ was added zinc perchlorate heptahydrate (33 mg, 90 μmol). The ligand slowly dissolved within 5 min. and the reaction was analyzed by means of ^{1}H NMR, which showed a quantitative formation of the complex. The solvent was removed under reduced pressure and the mixture was recrystallized from ethyl acetate/acetonitrile (1:1) by slow distillation of hexane into the solution (67 mg, 83 μmol, 95%): ^{1}H NMR (300 MHz, $CD_3CN/CDCl_3$): δ 2.2 (br, H_2O), 3.93 (s, 4H), 7.11 (m, 20H), 7.24 (d, *J* = 8.06 Hz, 2H), 7.48 (br, 2OH), 7.76 (dd, *J* = 8.06 Hz, *J* = 8.06 Hz, 2H), 7.87 (d, *J* = 8.06 Hz, 2H).). ^{13}C NMR: δ 45.03 (t), 82.87 (s), 119.94 (d), 125.56 (d), 127.55 (d), 127.66 (d), 128.55 (d), 140.95 (s), 142.00 (d), 146.76 (s), 157.50 (s).

Crystal structure of 8.9

Crystal Data: Formula: $[C_{38}H_{34}N_2O_3Zn]^{2-}.2[ClO_4]^-.C_4H_8O_2$, M = 400.29. Colorless transparent plate-shaped crystals of approximate dimensions of 0.10 x 0.42 x 0.43 mm were obtained by recrystallization from a mixture of ethyl acetate, acetonitrile and hexane. The asymmetric unit consists of four moieties: a cationic Zn-complex, two ClO_4^- anions and an ethyl acetate molecule. The crystals were monoclinic, *C*2/*c*, *a* = 34.79(1), *b* = 12.64(1), *c* = 18.181(2) Å, b = 90.17(2)°, *V* = 7995(7) Å^3, *Z* = 8, D_x = 1.527 gcm^{-3}, l(MoK$\bar{\alpha}$) = 0.71073 Å, μ = 8.2 cm^{-1}, *F*(000) = 3808 T = 130 K. *Data collection*: Although an X-ray structure determination was thwarted by persistent weak scattering crystals and also broad reflections, ultimately a data set was gathered by which a successful structure determination was accomplished. The data were collected on a Enraf-Nonius *CAD-4F*^{2} diffractometer, interfaced to a *INDY* (*Silicon Graphics*) *UNIX* computer (Mo tube, 50 kV, 40 mA, monochromated Mo-K$\bar{\alpha}$ radiation, Dw = 1.20) range 15.05° < q < 21.86°, reflections collected: independent reflections 2329. *Solution and refinement:* The structure was solved by direct methods with *SIR-97*.[23] Final refinement converged at *wR*(F^2) = 0.2459 for 3161 reflections and 546 parameters and *R*(*F*) = 0.0850 for 2329 reflections with $F_o \geq 4.0$.

Table 8.1: *Interatomic distances and selected bond angles for compound **8.9**.*

Interatomic Distances (Å)					
Zn(1)[a]	-O(1)	2.097(10)[b]	C(5)	-C(6)	1.520(18)
Zn(1)	-O(2)	2.055(9)	C(6)	-C(7)	1.52(2)
Zn(1)	-O(11)	2.003(10)	C(7)	-C(8)	1.51(2)
Zn(1)	-N(1)	2.040(11)	C(24)	-C(25)	1.52(2)
Zn(1)	-N(2)	2.081(12)	C(25)	-C(26)	1.56(2)
O(1)	-C(7)	1.418(16)	C(7)	-O(1)	1.418(16)
O(2)	-C(26)	1.442(15)	C(26)	-O(2)	1.442(15)
N(1)	-C(1)	1.364(17)	O(1)	-H(51)	0.9518
N(1)	-C(5)	1.353(15)	O(2)	-H(52)	0.9495
N(2)	-C(20)	1.372(18)	O(11)	-H(53)	0.9546
N(2)	-C(24)	1.353(16)	O(11)	-H(53')	0.9525
C(11)	-C(12)	1.40(2)	C(36)	-C(37)	1.36(2)
C(12)	-C(13)	1.39(3)	C(37)	-C(38)	1.46(2)

Bond angles (deg.)							
O(1)	-Zn(1)	-O(2)	86.3(4)	Zn(1)	-N(1)	-C(5)	125.3(9)
O(1)	-Zn(1)	-O(11)	103.6(4)	Zn(1)	-N(2)	-C(20)	112.6(8)
O(1)	-Zn(1)	-N(1)	88.2(4)	Zn(1)	-N(2)	-C(24)	125.9(9)
O(1)	-Zn(1)	-N(2)	147.7(4)	N(1)	-C(5)	-C(6)	117.0(11)
O(2)	-Zn(1)	-O(11)	101.2(4)	C(5)	-C(6)	-C(7)	117.(1)
O(2)	-Zn(1)	-N(1)	151.0(4)	O(1)	-C(7)	-C(6)	108.0(12)
O(2)	-Zn(1)	-N(2)	89.6(4)	N(2)	-C(24)	-C(25)	118.8(11)
O(11)	-Zn(1)	-N(1)	107.8(4)	C(24)	-C(25)	-C(26)	114.3(12)
O(11)	-Zn(1)	-N(2)	108.6(5)	O(2)	-C(26)	-C(25)	110.6(10)
N(1)	-Zn(1)	-N(2)	80.2(4)	Zn(1)	-O(1)	-H(51)	115.35
Zn(1)	-O(1)	-C(7)	129.4(9)	Zn(1)	-O(2)	-H(52)	117.37
Zn(1)	-O(2)	-C(26)	125.3(8)	Zn(1)	-O(11)	-H(53)	109.66
Zn(1)	-N(1)	-C(1)	113.9(8)	Zn(1)	-O(11)	-H(53')	109.53

Torsion angles (deg.)				
N(1)	-C(1)	-C(20)	-N(2)	6.4(18)

[a] The numbering for the crystal data does not follow the numbering used in nomenclature.

[b] Standard deviation in parentheses.

Copper complex of 8.2a

The phenanthroline diol **8.2a** (63 mg, 0.11 mmol) was suspended in acetonitrile and $Cu(acac)_2$ (30 mg, 0.11 mmol) was added and the material slowly dissolved. A blue precipitate was formed. The product was filtered and recrystallized from ethyl acetate blue crystals (45 mg, 0.07 mmol, 65%): ^{1}H NMR (300 MHz, $CDCl_3$): δ -17.5, -2.1, 1.0, 6.6, 9.5, 10.5, 35.0, 61.7. HRMS calcd 633.160; no proper HRMS could be obtained. Anal. Calcd for $C_{40}H_{30}N_2O_2Cu$: C, 75.75; H, 4.77; N, 4.42; Cu, 10.02. Found C, 75.11; H, 4.65; N, 4.35; Cu, 10.24.

Copper complex of 8.7a

The free ligand **8.7a** (50 mg, 91 μmol) was suspended in 3 mL of a mixture of acetonitrile and chloroform (2:1). $Cu(acac)_2$ (26 mg, 99 μmol) was added and stirring continued overnight. The solvents were removed and the product recrystallized from ethyl acetate to afford the di copper complex **8.9** (35 mg, 36 μmol, 40%): ^{1}H NMR (300 MHz, $CD_3CN/CDCl_3$): δ -7.5, -1.3, 1.2, 2.0, 4.1, 6.6, 9.5, 10.5, 34.7, 61.2.

Crystal Structure of 8.10

Crystal Data: Formula: $C_{42}H_{36}Cu_2N_2O_7.C_{42}H_{36}Cu_2N_2O_6.4[C_4H_8O_2]$, M = 1952.12. Bluish-green block-shaped crystals were obtained by recrystallization from ethyl acetate. The crystal, a parallelepiped of approximate size 0.25 x 0.30 x 0.50 mm., used for characterization and data collection was picked from the mother liquor. The asymmetric unit consists of two di-Cu complexes and four partly occupied and heavily disordered acetate molecules The crystal was monoclinic, *Cc*, *a* = 31.095(5), *b* = 16.683(2), *c* = 22.055(3) Å, b = 130.68(1)°, *V* = 8677(2) Å^3, *Z* = 4, D_x = 1.494 gcm^{-3}, l(MoK$\bar{\alpha}$) = 0.71073 Å, μ = 10.5 cm^{-1}, *F*(000) = 4064. Data collection: The data were collected on an Enraf-Nonius *CAD*-4*F*^{2} diffractometer, interfaced to an *INDY* (*Silicon Graphics*) *UNIX* computer (Mo tube, 50 kV, 40 mA, monochromated Mo-K$\bar{\alpha}$ radiation, Dw = 1.05 + 0.34 tg q), T = 130 K, range 11.13° < q < 16.17°. Reflections collected: independent reflections 5084. *Solution and refinement:* The structure was solved by Patterson methods and extension of the model was accomplished by direct methods applied to difference structure factors using the program *DIRDIF*. From the solution it was clear that the solvent molecules were highly disordered. The positional and anisotropic displacement parameters of the two di-nuclear Cu-complexes were refined. The refinement was complicated (frustrated) by the disorder problem. A subsequent difference Fourier synthesis showed residual density, not exceeding 1.9 e/Å^3, within the holes of the crystal lattice, which could be correlated to (partly) occupied and disordered acetate molecules. Enantiomorph twin refinement resulted in a value of 0.76(5). Final refinement on

F^2 carried out by full-matrix least-squares techniques converged at $wR(F^2)$ = 0.1272 for 6286 reflections and $R(F)$ = 0.0522 for 5084 reflections with F_o Å 4.0 $\sigma(F_o)$ and 946 parameters.

Table 8.2: *Interatomic distances and selected bond angles for compound **8.10**.*

Interatomic Distances (Å.); Residue: 1.					
Cu(1)[a]	-Cu(2)	3.151	O(5)	-C(41)	1.20(3)
Cu(1)	-O(1)	1.913(10)[b]	O(6)	-C(41)	1.30(3)
Cu(1)	-O(2)	1.913(9)	N(1)	-C(1)	1.373(18)
Cu(1)	-O(3)	2.342(7)	N(1)	-C(5)	1.331(14)
Cu(1)	-N(1)	1.954(10)	N(2)	-C(20)	1.349(17)
Cu(1)	-N(2)	2.000(11)	N(2)	-C(24)	1.338(14)
Cu(2)	-O(2)	1.943(8)	C(1)	-C(20)	1.491(15)
Cu(2)	-O(4)	1.947(10)	C(5)	-C(6)	1.50(2)
Cu(2)	-O(5)	1.921(11)	C(6)	-C(7)	1.546(18)
Cu(2)	-O(14)	1.965(9)	C(24)	-C(25)	1.486(19)
O(1)	-C(7)	1.406(12)	C(25)	-C(26)	1.56(2)
O(2)	-C(26)	1.444(12)	C(39)	-C(40)	1.51(3)
O(3)	-C(39)	1.235(15)	C(41)	-C(42)	1.55(4)
O(4)	-C(39)	1.267(17)			

Bond angles (deg.); Residue: 1.							
O(1)	-Cu(1)	-O(2)	89.7(4)	Cu(1)	-O(2)	-Cu(2)	109.6(3)
O(1)	-Cu(1)	-O(3)	96.1(3)	Cu(1)	-O(2)	-C(26)	123.4(8)
O(1)	-Cu(1)	-N(1)	95.2(4)	Cu(2)	-O(2)	-C(26)	120.3(6)
O(1)	-Cu(1)	-N(2)	161.5(3)	Cu(1)	-O(3)	-C(39)	114.1(7)
O(2)	-Cu(1)	-O(3)	86.7(3)	Cu(2)	-O(4)	-C(39)	106.7(7)
O(2)	-Cu(1)	-N(1)	174.8(4)	Cu(2)	-O(5)	-C(41)	127.2(12)
O(2)	-Cu(1)	-N(2)	94.2(4)	Cu(1)	-N(1)	-C(1)	116.4(7)
O(3)	-Cu(1)	-N(1)	91.0(3)	Cu(1)	-N(1)	-C(5)	124.9(9)
O(3)	-Cu(1)	-N(2)	102.2(4)	Cu(1)	-N(2)	-C(20)	113.7(7)
N(1)	-Cu(1)	-N(2)	81.7(4)	Cu(1)	-N(2)	-C(24)	126.5(10)
O(2)	-Cu(2)	-O(4)	94.0(4)	C(20)	-N(2)	-C(24)	119.0(11)
O(2)	-Cu(2)	-O(5)	162.6(4)	O(3)	-C(39)	-O(4)	123.0(13)
O(2)	-Cu(2)	-O(14)	86.3(3)	O(3)	-C(39)	-C(40)	119.4(13)
O(4)	-Cu(2)	-O(5)	91.7(5)	O(4)	-C(39)	-C(40)	117.5(12)
O(4)	-Cu(2)	-O(14)	157.1(4)	O(5)	-C(41)	-O(6)	126.(2)
O(5)	-Cu(2)	-O(14)	94.8(4)	O(5)	-C(41)	-C(42)	119.1(18)
Cu(1)	-O(1)	-C(7)	122.3(9)				

Interatomic Distances (Å.); Residue: 2.					
Cu(3)	-Cu(4)	2.8861(18)	O(10)	-C(89)	1.284(13)
Cu(3)	-O(7)	1.908(8)	O(11)	-C(91)	1.285(14)
Cu(3)	-O(8)	1.986(9)	O(12)	-C(91)	1.269(15)
Cu(3)	-O(9)	2.206(7)	N(3)	-C(51)	1.341(14)
Cu(3)	-N(3)	1.978(10)	N(3)	-C(55)	1.352(18)
Cu(3)	-N(4)	1.968(10)	N(4)	-C(70)	1.365(14)
Cu(4)	-O(7)	2.225(9)	N(4)	-C(74)	1.341(19)
Cu(4)	-O(8)	1.932(8)	C(51)	-C(70)	1.49(2)
Cu(4)	-O(10)	1.928(7)	C(55)	-C(56)	1.540(15)
Cu(4)	-O(11)	2.073(7)	C(56)	-C(57)	1.513(15)
Cu(4)	-O(12)	2.001(9)	C(74)	-C(75)	1.534(16)
Cu(4)	-C(91)	2.384(12)	C(75)	-C(76)	1.501(15)
O(7)	-C(57)	1.409(16)	C(89)	-C(90)	1.515(13)
O(8)	-C(76)	1.417(16)	C(91)	-C(92)	1.484(18)
O(9)	-C(89)	1.223(14)			

Bond angles (deg.); Residue: 2.							
Cu(4)	-Cu(3)	-O(7)	50.4(3)	Cu(3)	-N(4)	-C(70)	115.4(9)
Cu(4)	-Cu(3)	-O(8)	41.8(2)	Cu(3)	-N(4)	-C(74)	125.8(7)
Cu(4)	-Cu(3)	-O(9)	77.7(2)	C(70)	-N(4)	-C(74)	118.5(10)
Cu(4)	-Cu(3)	-N(3)	147.5(3)	N(3)	-C(51)	-C(52)	120.8(13)
Cu(4)	-Cu(3)	-N(4)	130.7(3)	N(3)	-C(51)	-C(70)	114.9(10)
O(7)	-Cu(3)	-O(8)	86.0(4)	C(52)	-C(51)	-C(70)	124.2(11)
O(7)	-Cu(3)	-O(9)	94.9(3)	C(51)	-C(52)	-C(53)	118.8(12)
O(7)	-Cu(3)	-N(3)	97.1(4)	C(52)	-C(53)	-C(54)	120.0(15)
O(7)	-Cu(3)	-N(4)	172.6(3)	C(53)	-C(54)	-C(55)	120.0(16)
O(8)	-Cu(3)	-O(9)	94.1(3)	N(3)	-C(55)	-C(54)	120.2(11)
O(8)	-Cu(3)	-N(3)	157.8(3)	O(11)	-Cu(4)	-C(91)	32.6(4)
O(8)	-Cu(3)	-N(4)	92.4(4)	O(12)	-Cu(4)	-C(91)	32.2(4)
O(9)	-Cu(3)	-N(3)	107.5(4)	Cu(3)	-O(7)	-Cu(4)	88.2(4)
O(9)	-Cu(3)	-N(4)	92.3(4)	Cu(3)	-O(7)	-C(57)	120.7(6)
N(3)	-Cu(3)	-N(4)	81.7(4)	Cu(4)	-O(7)	-C(57)	148.8(6)
Cu(3)	-Cu(4)	-O(7)	41.4(2)	Cu(3)	-O(8)	-Cu(4)	94.9(5)
Cu(3)	-Cu(4)	-O(8)	43.3(3)	Cu(3)	-O(8)	-C(76)	126.1(6)
Cu(3)	-Cu(4)	-O(10)	83.4(2)	Cu(4)	-O(8)	-C(76)	124.8(6)
Cu(3)	-Cu(4)	-O(11)	119.38(19)	Cu(3)	-O(9)	-C(89)	124.8(7)
Cu(3)	-Cu(4)	-O(12)	155.3(3)	Cu(4)	-O(10)	-C(89)	130.2(6)

Cu(3)	-Cu(4)	-C(91)	147.5(3)	Cu(4)	-O(11)	-C(91)	87.2(6)
O(7)	-Cu(4)	-O(8)	79.1(4)	Cu(4)	-O(12)	-C(91)	90.8(7)
O(7)	-Cu(4)	-O(10)	97.1(3)	Cu(3)	-N(3)	-C(51)	114.9(9)
O(7)	-Cu(4)	-O(11)	100.2(3)	Cu(3)	-N(3)	-C(55)	124.9(7)
O(7)	-Cu(4)	-O(12)	115.2(4)	O(9)	-C(89)	-O(10)	123.3(8)
O(7)	-Cu(4)	-C(91)	113.0(4)	O(9)	-C(89)	-C(90)	120.6(10)
O(8)	-Cu(4)	-O(10)	98.1(3)	O(10)	-C(89)	-C(90)	116.(1)
O(8)	-Cu(4)	-O(11)	99.7(3)	Cu(4)	-C(91)	-O(11)	60.3(5)
O(8)	-Cu(4)	-O(12)	159.5(4)	Cu(4)	-C(91)	-O(12)	57.0(6)
O(8)	-Cu(4)	-C(91)	130.3(4)	Cu(4)	-C(91)	-C(92)	175.7(9)
O(10)	-Cu(4)	-O(11)	157.2(3)	O(11)	-C(91)	-O(12)	117.(1)
O(10)	-Cu(4)	-O(12)	94.6(3)	O(11)	-C(91)	-C(92)	123.8(11)
O(10)	-Cu(4)	-C(91)	125.7(4)	O(12)	-C(91)	-C(92)	119.1(12)
O(11)	-Cu(4)	-O(12)	64.6(3)				

Torsion angles (deg.)					
Residue 1	N(1)	-C(1)	-C(20)	-N(2)	-5.1(14)
Residue 2	N(3)	-C(51)	-C(70)	-N(4)	-4.2(12)

[a] The numbering for the crystal data does not follow the numbering used in nomenclature.

[b] Standard deviation in parentheses.

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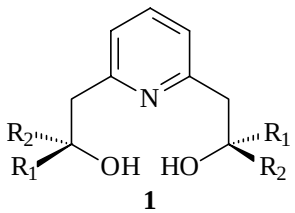
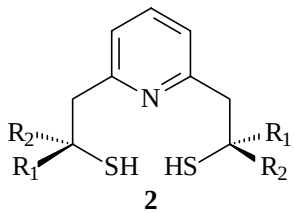
SAMENVATTING

Enzymen spelen in het leven van mens, dier en plant een enorm grote rol. Enzymen zijn biologische katalysatoren dwz. versnellers van (bio)chemische processen die zich in levende organismen afspelen. Enzymen zijn eiwitten die opgebouwd zijn uit aminozuren. Voor de werking van enzymen speelt het actieve centrum een belangrijke rol. In dit gedeelte van het enzym vindt de binding met de om te zetten stof (substraat) en de uiteindelijke reactie plaats. Enzymen bezitten een grote mate van selectiviteit zodat niet elke stof in dit actieve centrum gebonden kan worden en dus niet elke stof omgezet kan worden. Voor bijna elke biochemische reactie bestaat een afzonderlijk enzym. Zo zijn er enzymen voor oxidatie en reductie reacties: de oxidoreductases. Verder zijn er transferases, enzymen die de overdracht van een groep van de ene stof op de andere katalyseren. Ook hydrolasen, lypasen, isomerasen, ligasen en dehydrogenasen komen voor.
Tegenwoordig is men in staat enzymen te winnen uit bijvoorbeeld planten, schimmels, gisten en slachtafval, zodat deze gebruikt kunnen worden in de chemische industrie. In de bio-organische chemie wordt veel onderzoek verricht naar de mogelijkheden van het gebruik van enzymen buiten de organismen. Maar ook wordt veel onderzoek gedaan naar de precieze werking van enzymen. Om meer inzicht te krijgen in de werking van enzymen worden modellen van het actieve centrum gemaakt en bestudeerd. Modellen zijn over het algemeen kleiner dan de enzymen zelf en zijn hierdoor beter te bestuderen. Ook het aanbrengen van variaties voor het regelen van de substraatselectiviteit is hierdoor vergemakkelijkt. Aan de hand van enzymmodellen is het ook mogelijk om nieuwe katalysatoren voor chemische reacties te ontwikkelen. In dit proefschrift wordt het onderzoek beschreven naar enzym modellen van een alcohol dehydrogenase en naar katalysatoren op basis van pyridine die uit dit onderzoek naar voren gekomen zijn. Hierop zal ik hieronder in detail verder ingaan.

In hoofdstuk 1 wordt een inleiding gegeven over enzymen en over *horse liver alcohol dehydrogenase* (HLADH) in het bijzonder. Een aantal bekende modellen van dit enzym wordt besproken. Mogelijke verbeteringen voor de ontwikkeling van een model worden aangedragen. In het tweede deel van dit hoofdstuk wordt ingegaan op pyridine diolen **1** en pyridine dithiolen **2**. Deze verbindingen lijken door hun complexatie-eigenschappen een goed uitgangspunt voor de ontwikkeling van (bio)katalysatoren.

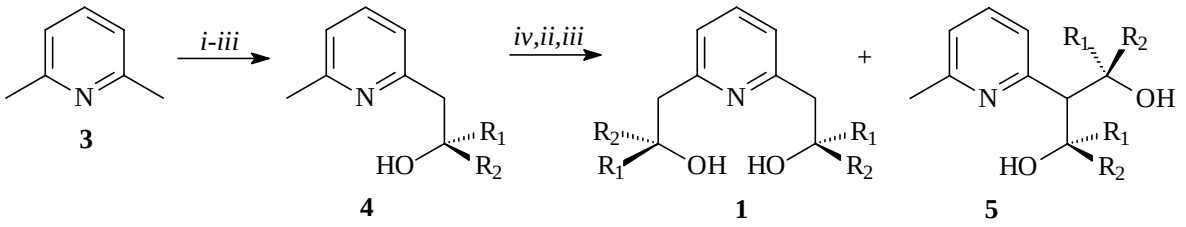


1



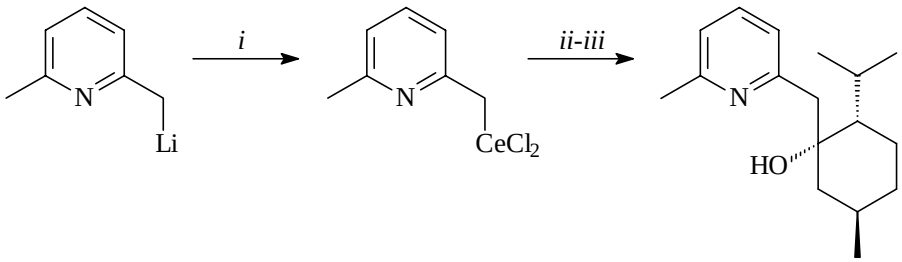
2

In hoofdstuk 2 wordt de synthese van pyridine diolen **1** onder de loep genomen. Uit het onderzoek is gebleken dat het het meest rendabel is om deze verbindingen in twee stappen te maken (als aangegeven in Schema 1).[1]



Schema 1 *Reagentia en condities: i, n*-BuLi (1.1 equiv.), THF, -60 °C; *ii* $R_1R_2C=O$; *iii* 2N HCl; *iv n*-BuLi (2.1 equiv.), THF, rt.

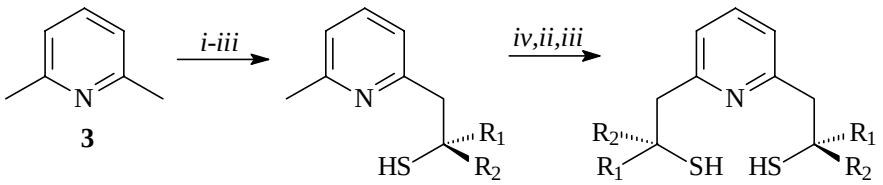
In een eerste stap wordt 2,6-lutidine **3** via een base-geïnduceerde reactie gederivatiseerd op een van de methylgroepen tot het pyridine alcohol **4**, vervolgens wordt in een tweede stap de andere methylgroep gederivatiseerd tot het pyridine diol **1**. Uit het onderzoek bleek bovendien dat er in meer of mindere mate een bijproduct **5** gevormd wordt waarin de tweede derivatisering aan dezelfde kant heeft plaatsgevonden als de eerste. Dit tot nu toe onbekende product is in sommige gevallen niet stabiel en retro-additie geeft vervolgens het tussenproduct **4** weer terug. Door het gebruik van kalium diisopropylamide als base kan de vorming van het nevenproduct **5** tegengegaan worden. Chirale pyridine alcoholen kunnen gesynthetiseerd worden uitgaande van kamfer, fenchon of menthone. De reactie aan kamfer is regioselectief. De reactie aan menthone en fenchon geeft een mengsel van *cis*/*trans* cq. *endo*/*exo* producten. Door gebruik te maken van metaal uitwisseling tussen lithium en cerium bij toevoeging van $CeCl_3$ na deprotoneren van 2,6-lutidine en vervolgens additie van menthone is het mogelijk om de reactie regioselectief te laten verlopen (Schema 2).



Schema 2 *Reagentia en condities: i*,$CeCl_3$·THF, -70°C, *ii* (-)-menthone; *iii* 2N NH_4Cl.

In hoofdstuk 3 wordt een nieuwe methode voor de synthese van pyridine thiolen besproken.[2] Een directe base-geïnduceerde additie van 2,6-lutidine **3** aan thioadamantanone en thiofenchone geeft de gewenste pyridine thiolen **6** en dithiolen **2**. De additie aan thiofenchon verliep geheel regioselectief dit in tegenstelling tot de additie aan fenchon zelf. De synthese

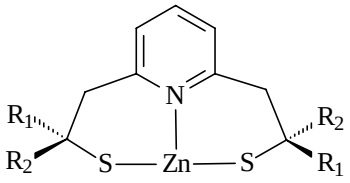
van pyridine thiolen gebaseerd op enolisatie gevoelige thioketonen is mogelijk door gebruik te maken van grignard reagentia.



3 **6** **2**

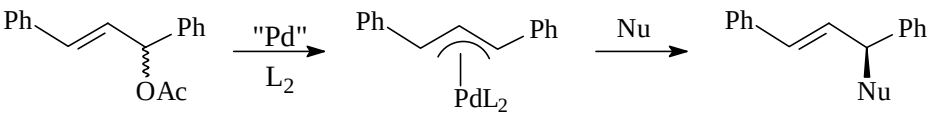
Schema 3 *Reagentia en condities*: *i, n*-BuLi (1.1 equiv.), THF, –80°C; *ii* $R_1R_2C=S$; *iii* H_3O^+; *iv n*-BuLi (2.1 equiv.), THF, –80 °C.

In hoofdstuk 4 worden complexen van de pyridine alcoholen **1** en thiolen **2** met verschillende zuren beschreven.[2] Deze pyridine alcoholen **1** en thiolen **2** zijn goed in staat om HCl, HBr en HNO_3 te binden in de holte van het molecule. Naast het complexeren van zuren zijn deze verbindingen prima in staat om complexen te vormen met zink. Het thioadamantanon gebaseerd pyridine thiol gaf een dimeer complex, terwijl het thiofenchon gebaseerde pyridine thiol bij complexatie met zinknitraat een monomeer zink complex **7** bleek te vormen. Dit lijkt een uitstekend uitgangspunt als model voor HLADH. Hierop wordt in hoofdstuk 7 verder ingegaan.



7

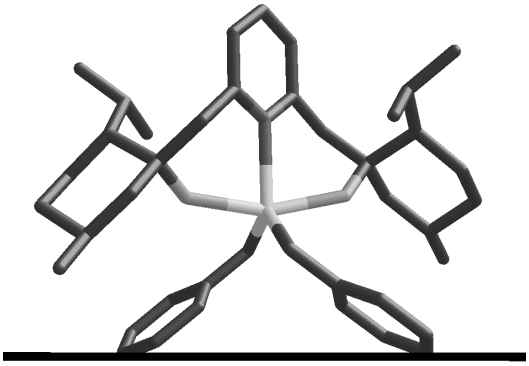
In hoofdstuk 5 worden de chirale pyridine thiolen **6** en dithiolen **2** hun thioether analoga getest in de palladium gekatalyseerde allylische substitutie (Schema 4).[3] Daar waar de thiolen inactief zijn geven de thioethers hoge enantiomere overmaat in de omzetting van het substraat. Aan de hand van een geïsoleerd intermediair werd het mechanisme voor de overdracht van de chiraliteit van de katalysator op het substraat nader bekeken.



Schema 4 *De palladium gekatalyseerde allylische substitutie*

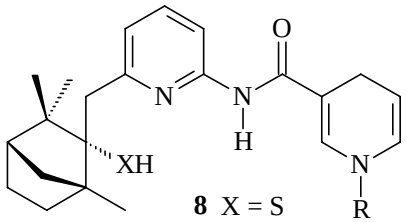
In hoofdstuk 6 worden de chirale pyridine alcoholen en thiolen getest in een combinatoriële variant van de diethylzink additie aan aldehydes. Middelmatige tot goede selectiviteiten werden gevonden bij het gebruik van de pyridine alcoholen **4** en thiolen **6**. De diolen **1** en

dithiolen **2** waren praktisch inactief door de sterke complexatie van zink. In het tweede gedeelte van dit hoofdstuk wordt de synthese van een polymerisatie katalysator gebaseerd op een pyridine diol **1** beschreven.[4] Complexatie van het menthone gebaseerde diol **1** met zirkonium gaf een actieve katalysator voor de polymerisatie van propyleen (Figuur 1). Het gevormde polymeer bleek atactisch te zijn.



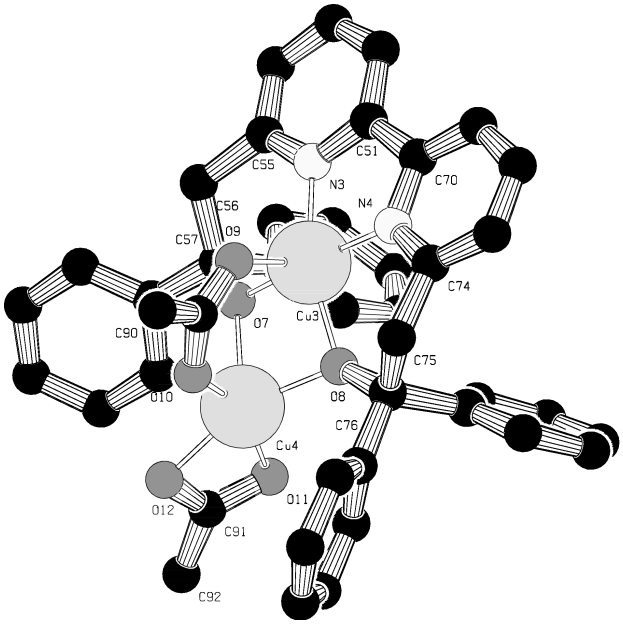
Figuur 1 *Resultaat van semi-empirische berekeningen met een PM3(tm) model.*

In hoofdstuk 7 blijkt het gesynthetiseerde monomeer zink complex **7** niet actief te zijn als model voor HLADH. Waarschijnlijk is het complex niet in staat zowel het substraat als het coenzyme-model (een 1,4-dihydropyridine) bij elkaar te brengen. Modificatie van het model door koppeling van een 1,4-dihydropyrisine aan een pyridine thiol blijkt een actief model **8** te geven. Dit model reduceert ethyl phenylglyoxylate in de aanwezigheid van $Mg(ClO_4)_2$ in slechts 15 min. Ook het pyridine alcohol analoog **9** gaf een snelle reductie, waarna het gevormde alcohol door nog onbekende oorzaak weer langzaam terug oxideert naar het keton.



8 X = S
9 X = O

In hoofdstuk 8 wordt de methode voor de synthese van pyridine alcoholen toegepast voor de derivatisering van fenanthrolines en bipyridines. Derivatisering met benzophenon en adamantanon verlopen gelijk aan de pyridine analoga. Derivatisering met kamfer behoeft een metaal uitwisseling van lithium met cerium. Complexaties met zink en koper verlopen goed. Het omkristalliseren van het kopercomplex uit ethyl acetaat leidde tot de hydrolyse van het oplosmiddel en de vorming van onderstaand bis-koper complex **10**.



Figuur 2 *X-ray structuur van het koper complex **10**.*

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